CORONARY HEART DISEASE

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BLACKWELL
SCIENTIFIC PUBLICATIONS
Oxford

Published and copyrighted 1959 in the United States of America by
CHARLES C THOMAS · PUBLISHER
301-327 East Lawrence Avenue, Springfield, Illinois.

Published simultaneously in Canada by
THE RYERSON PRESS
Queen Street West, Toronto 2.

Printed in the United States of America

TO

My Dedicated Medical Science Colleagues
Whose Labors Underlie
Much of the Data in this Volume

PREFACE

Medical scientific researches into the origins and causes of diseases have a highly practical goal, the earliest possible application of findings in the prevention and treatment of such diseases in humans. To be sure, all who work in medical research are ... an academic curiosity concerning nature which is a ... work. But abundant ... ults can be translated ... of the new knowledge for the ben...

At times, in the history of investigation of certain diseases, knowledge is so fragmentary as to preclude its reduction to practical, clinical utilization This is not the case for coronary heart disease A tremendous fund of knowledge has been accumulated through the extensive investigations of workers throughout the world. Unfortunately, however, the pertinent discoveries are scattered throughout a host of journals Further, there has been all too little effort to integrate the various discoveries into an overall concept of the evolution of sub-clinical coronary heart disease into its serious clinical sequelae. With full realization that much remains to be discovered, an attempt has been made here to integrate today's knowledge into a working concept that the clinician can use now in his practise. There seems little reason to doubt that clinical application of what we already know can make a massive dent in the high morbidity and mortality resulting from coronary heart disease As new knowledge becomes available, its application at the clinical level will be greatly facilitated in the ... ...ch knowledge ... his book is for the clinician, written in the hope that he will find it useful in his daily effort directed toward minimization of premature clinical coronary heart disease

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ACKNOWLEDGMENTS

Some aspects of modern medical investigation are very costly of originality, ideas, time, equipment, and much hard labor. In such endeavors many workers contribute in each such area, and often to an extent unrealized when data are reduced to a relatively few pertinent conclusions Underlying the clinical approach to coronary heart disease set forth in this book is an experience with some seventy thousand analyses of human bloods by ultracentrifugal and chemical methods. This has been possible primarily because of real devotion of certain people to the work. Among the outstanding people to whom the author owes real gratitude are Oliver deLalla, Alice deLalla, Virginia Dobbin, Harold Elliott, Keith Freeman, Frank Glazier, Thomas Hayes, Hardin Jones, Erma Kovich, Frank Lindgren, Alex Nichols, Francis Pierce, Leonard Rubin, Bernard Shore, Beverly Strisower, Edward Strisower, Arthur Tamplin, Robert Tandy, and Wei Young. Dolores Piluso and Margaret Mirk provided secretarial assistance well beyond any reasonable expectation. Many technicians have throughout ten years helped materially with several aspects of the research.

JOHN W. GOFMAN

INTRODUCTION

Coronary heart disease may be considered to be characterized by two major aspects or two major phases of development and manifestation. One phase is almost wholly, or wholly, at the sub-clinical level. The other represents a phase of coronary heart disease characterized by acute symptomatic and sign-laden manifestations With respect to the manifest phase of coronary heart disease excellent books are available concerning appropriate procedures for diagnosis of extent of cardiac injury, care of patients, and prognosis of acute episodes. Thus, for the management of myocardial infarction during the acute period with its features of shock, the possibility of heart failure, the arrhythmias, and embolization, standard medical practice and excellent text books of cardiology are fully adequate to provide the physician with the information he requires On the other hand with respect to the sub-clinical phase of coronary disease, whether that sub-clinical phase be *before* the first overt manifestation or during the period *between* clinical manifestations there exists a great void Partly, this is so because the significant research and development work, which creates the possibility for detection of the sub-clinical phase of coronary heart disease and for practical and constructive action during it, is very recent, and not available in medical texts. It is in this area where the physician feels a real need for information

Perhaps the essence of the problem which physicians face in handling coronary heart disease in the sub-clinical phase is the realization that during this phase the patient is not truly a patient in the usual therapeutic medical sense. While it is true that both the physician population and the population-at-large have become aware of the need in many areas for preventive medicine, it is only too true that generally such awareness for the need of preventive medicine really represents only lip-service. Who are the patients with sub-clinical coronary heart disease, how do we find them, and which of them are in need of management? These are questions that we must seriously address ourselves to as physicians if we are to make any serious inroads upon the problem of the mortality and morbidity caused by prema-

ture coronary heart disease. That this mortality is a very large one in our society is well-known to every physician, the facts being of course that coronary heart disease represents the number one adult cause of mortality in our Western civilization today. The very size of the clinical problem suggests that a large number of individuals must be considered as potential candidates for coronary heart disease. Indeed there appears to be no group which on *a priori* grounds can be regarded as free from the hazards of premature coronary heart disease. Secondly, a major characteristic of coronary heart disease is that it passes from a sub-clinical level, at which time it is silent and unknown to the patient and physician, into a clinically manifest state where its effects may be rapidly disastrous and fatal. At the present moment we cannot discern for any individual when he will pass from the sub-clinical state to the manifest state of coronary heart disease. Hence, when he does, surprise is generally occasioned that an individual in such apparently excellent health now develops signs and symptoms of a grave disease. This fact in itself points up the crucial need for dealing with coronary heart disease as a medical problem in the *sub-clinical phase* if we are to make real inroads in our attack upon it For, if we wait for signs and symptoms to become manifest, we know full well the limitations of the armamentarium available to us. On the other hand, if significant progress can be made with respect to delaying or preventing the evolution of the sub-clinical disease to the point where it becomes clinically manifest, we will have handled this disease in the most effective manner, heading off that phase of the disease which is so difficult to treat successfully and where so much appears to reside in the hands of fate and chance

For some reason there still exists in many medical quarters an opinion, a voiced opinion in fact, that we do not know anything at all about the background period *before clinically-manifest* coronary heart disease develops The only possibility that such a statement can be made in sincerity is an almost total ignorance of a body of medical and scientific facts which has been won at great cost over the past decade. In the author's opinion we now have a great deal of information concerning this critical sub-clinical period in the evolution of coronary heart disease.

Furthermore, such information is in a form such that reasonable approaches can be made toward its use for the purpose of preventing the early evolution of the clinical phase of this disease. The preventive methods available to us, at this moment, are undoubtedly not the best. Second, our knowledge, though much further ahead than is admitted by certain so-called authorities and experts, is riddled with gaps which need urgently to be filled. These gaps will be filled in part or in whole by further investigation both at the laboratory level and at the clinical level. However, there is every reason today to take advantage of the facts that we do have at our disposal and to move in the directions in which these facts lead us The intelligent application of available knowledge would surely lead to a sizable early reduction in the mortality due to coronary heart disease. As our information becomes broader, and as known gaps are filled, not only will the steps we have taken have already cut mortality, but they will in addition have readied us for earlier understanding and utilization of new findings From the point of view of the service the physician can perform and from the point of view of the advantage to his patient, there is every reason to do now what we can with available knowledge to attempt to reduce coronary disease mortality. There is perhaps an even greater dividend that would arise out of the early awareness of every physician concerning what can be done about coronary disease in its subclinical phases *at this time* and of all physicians initiating active steps to prevent this disease For, if the large bulk of the medical profession realizes what we do know about coronary heart disease and starts now applying this knowledge to the prevention of coronary disease, it is inevitable that this work itself in the preventive aspect of coronary heart disease will lead them to observations, to trials of management programs, and to experimental work which will materially advance our knowledge. With every physician being in direct contact with the problem through consistent application of current knowledge we would have many more brains at work toward an ultimate definitive solution This is certain to prove rewarding. For a physician to invest effort in the prevention of coronary heart disease with what knowledge we do have now means that the physician must

understand fully the tremendous recent advances in our knowledge as well as the limitations of that knowledge. He must understand what is very solidly-based, what is hypothesis, what is in the realm of experimental medicine. The information in these areas needs to be assembled in one place, so that the physician can see the picture as a whole. It is the purpose and the endeavor of the author of this book to provide such information to the physician together with a program which he can apply himself in his current effort to reduce the mortality from coronary heart disease.

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CORONARY HEART DISEASE

Chapter I

CLINICAL CORONARY HEART DISEASE AND CORONARY ARTERY ATHEROSCLEROSIS

CORONARY heart disease is a clinical entity; coronary atherosclerosis (or arteriosclerosis), a pathological entity. A considerable body of scientific evidence links these two entities Yet much confused thinking is generated because of the failure to separate them and to realize their truly separate natures: Indeed, major elements of the progress made in the understanding of clinical coronary heart disease and its prevention have been possible only by a separation of the considerations of these two entities

CORONARY ARTERY ATHEROSCLEROSIS

The coronary arteries, along with medium-sized arteries elsewhere in the body, are the seat of a disease process characterized by a thickening of the intimal coat of the arterial wall The normal, undiseased coronary artery has practically no tissue in the intimal layer between the endothelial lining and the internal elastic membrane The pathologic essence of the major disease process which affects the coronary arteries is an accumulation of inert material and tissue within this intimal coat, internal to the internal elastic membrane Diverse chemical and structural elements are found to make up the material which accumulates within the intima of diseased coronary arteries Among these materials are lipids of various sorts, calcium salts and even calcium in the form of bone, fibrous and fibro-elastic tissue, hemorrhagic areas, and areas of thrombosis at various stages of organization

There exist several views concerning the pathogenetic sequence of events in the development of the mature arterial lesion. Largely such views differ with respect to the early stages of the development of the lesion and with respect to the structural feature considered as primary. One concept attributable to Rokitansky[1], and more recently to Duguid[2], is that thrombosis is the primary event in the artery and that the remaining morphologic features of the lesion are in some way a later result of such thrombosis. A second view, originating with Winternitz, Thomas, and Le Compte[3], holds that hemorrhage into the intimal part of the artery wall from vasa vasora is the primary process, all other features representing various aspects of the tissue reaction to such hemorrhage. A third view is centered around the lipid elements of the arteriosclerotic lesion. Anitschkow[4] proposed that lipids from the circulating blood infiltrate through the endothelial lining and there set up the original lipid deposits which initiate reactive changes on the part of the body with ultimate development of the full-blown lesion. More recently, there is the view of Rinehart and Moon[5] that alterations in the mucopolysaccharide structure of the ground substance of the arterial wall is the initiating feature of the lesion and that the other aspects of the lesion are secondary to this. In support of each of these various views there are structural features and elements of biological evidence which suggest possible validity. Unfortunately, however, the proponents of each of the views concerning the primary materials which constitute the arteriosclerotic deposit have felt at times the necessity of insisting upon that primacy to the absolute exclusion of all other possibilities What is worse they have misinterpreted their privileges in this regard in that by insistence on a particular view of the primary structural element they have stated directly or indirectly that an entire body of biochemical, clinical, and other evidence (which body of evidence is entirely self-sufficient) must be incorrect. One is certainly entitled to entertain any view of the primary facets involved in development of the arteriosclerotic lesion It is encouraging that various investigators have given much thought to possible modes of pathogenesis of this disease, but when such views are used to run head-on into solidly-established clinical and biochemical evidence, we reach an impass which is patently ridicu-

lous. A *view* which is clearly in opposition with *facts* simply needs modification because it cannot be correct. It may not be completely incorrect but it certainly needs modification.

Perhaps a more fruitful approach to the entire problem is to recognize the existence of various structural features of the coronary arteriosclerotic lesion and to look forward to the time when an integrated concept of the origin and pathogenesis of this disease will allow for the proper placement of each such structural feature. Insistence upon primacy of a particular feature at a time when such primacy cannot be established can serve only to impede progress which would otherwise be possible. It is largely from considerations such as these that the author of this book prefers the term used by Goldblatt[6] to describe this lesion, namely, "simple intimal arteriosclerosis" rather than "atherosclerosis." In this way one eliminates the prejudicial view that the lipid element of the lesion is either primary or most important as is suggested by the origin of the term "athero." Many of the arterial lesions show very little lipid at that particular point in time when the pathologist has the opportunity to examine the tissue. Unfortunately, when such lesions are termed "atherosclerotic lesions," certain investigators take great offense because they can argue that there is no "athero" element to be found. Such controversy can be eliminated by the use of the term "simple intimal arteriosclerosis" to encompass at this time those lesions which result in the accumulation of tissue or inert material between the internal elastic membrane and the lumen of the artery and which have the ultimate effect of narrowing the lumen of that artery.

It is now fairly widely agreed as a result of careful pathological studies, including the injection studies of gross specimens, such as the classical ones of Blumgart and Schlesinger[7], the microscopic pathological studies of Spain and co-workers[8], and of Dry, Edwards and White[9] that coronary arteriosclerosis is quantitatively related to the clinical manifestations of coronary heart disease. In Blumgart and Schlesinger's very beautiful injection studies it was clearly shown that, in the presence of clinical coronary heart disease in the form of angina pectoris or myocardial infarction, the coronary arteries at post-mortem examination show extensive arteriosclerosis, a degree of arteriosclerosis definitely *in excess* of that found in

patients without such clinical disease. This is so despite the fact that essentially all so-called "healthy" individuals show some degree (and often a marked degree) of coronary arteriosclerosis. The important issue is not that the apparently healthy individuals do show *some* coronary arteriosclerosis, but rather that they show a lesser extent of this process, on the average, than do those individuals with overt clinical coronary heart disease. In a careful study of post-mortem material from individuals dying in the age range from 26-40 years of age, Spain showed clearly that the average degree of narrowing of the coronary arteries due to accumulation of arteriosclerotic tissue in the intima was very much greater in individuals who died of myocardial infarction than in those who died accidentally of a variety of causes other than clinical heart disease

The studies of Dry, Edwards and White provided similar findings of an excessive degree of coronary arteriosclerosis in persons with clinically-manifest coronary heart disease. None of these findings call for an insistence that every case of clinical coronary heart disease, either in the form of angina pectoris, coronary insufficiency, or myocardial infarction, necessarily rests upon an etiology of coronary arteriosclerosis, although it is quite clear that the vast majority of such cases are significantly associated with coronary arteriosclerosis Some authors have considered coronary arteriosclerosis to be the etiology of as many as 95 per cent of cases of clinical coronary heart disease, while others have suggested somewhat lower percentages than this. Other possible pathological bases for clinical coronary heart disease have involved such features as (1) rheumatic or syphilitic involvement of the coronary artery ostia, (2) anomalous origin of one or more of the coronary arteries, as from the pulmonary arteries, and (3) anomalous congenital stenotic lesions of the coronary arteries This entire latter group of possibilities is regarded in present-day coronary heart disease material not to constitute anything more than perhaps 10 per cent of the total basis for clinical coronary heart disease. Thus it seems quite clear that coronary arteriosclerosis is the major underlying lesion present in the arteries related to the development of clinical coronary heart disease. However, this fact has created a certain amount of confusion in

the mind of certain investigators who doubt the etiologic significance of coronary arteriosclerosis and who misunderstand its relationship with the clinical disease. One such misconception is that which centers around the widespread occurrence of coronary arteriosclerosis in the adult population of a country like the United States

It is perfectly true that if one were to examine the coronary arteries of a large group of 50 year old United States males in health, one would find an appreciable average involvement of such arteries with arteriosclerosis. Indeed some of the individuals in apparent health will show a greater degree of coronary artery arteriosclerosis and attendant narrowing than will certain individuals of the same age and sex who have suffered one, two, three, or even four myocardial infarctions An erroneous conclusion that has been drawn by some is that coronary arteriosclerosis cannot be very important if individuals in apparent health can have, at times, more coronary arteriosclerosis than individuals who have overt clinical coronary heart disease. We do know now that, on the average, the degree of coronary arteriosclerosis is higher in individuals with clinical coronary heart disease than it is in otherwise comparable individuals without clinical coronary heart disease But what we must realize urgently is that individuals who are in apparent health today are fully entitled to show varying degrees of coronary arteriosclerosis, some very extensive degrees, some moderate degrees, and some *minimal* degrees. This in no way contradicts the relationship of coronary arteriosclerosis with the clinical entity, coronary heart disease.

First, it is important to realize that the individuals *in apparent health today* at age 50 years represent the prime substrate out of which grow the individuals who later become labelled "individuals with overt clinical coronary heart disease." Certainly if coronary arteriosclerosis is etiologically related to clinical coronary heart disease, it is essential that many so-called healthy individuals must be developing coronary arteriosclerosis, for otherwise we would never see any *new* cases of clinical coronary heart disease. This latter is unfortunately not the case, inasmuch as the clinical entity continues to develop in alarming proportions in our population every day. The true nature of the

relationship of coronary arteriosclerosis and clinical coronary heart disease is really that, with an increasing average degree of coronary arteriosclerosis, the *risk* of a clinical manifestation such as angina pectoris, coronary insufficiency, myocardial infarction, or heart failure becomes progressively greater. It is important to underline that this is a *risk* of such a clinical event becoming greater. It is *not* an absolute certainty nor is it an absolute certainty *in any specified time interval.* The matter might be put this way. If one were able to segregate two groups of individuals in the population, both groups being in apparent health, with one group showing an extensive degree, on the average, of coronary arteriosclerosis and the other showing a minimal average degree of coronary arteriosclerosis, and then could follow both groups for some time period, e.g., one month, one year, or ten years, the following would be true. There would be more cases of clinical coronary heart disease appearing in the group with extensive coronary arteriosclerosis than there would be in the group with minimal coronary arteriosclerosis. Furthermore, the wider the separation in average degree of coronary arteriosclerosis between the two groups the wider will be the disparity in numbers of individuals who develop a clinical manifestation of coronary heart disease in any particular time period.

Precisely why it is that one individual with a particular degree of coronary arteriosclerotic involvement has a clinical episode at some period in life and another avoids such an episode for some extended period beyond that is not at all clear at the present moment. It is entirely possible that this will not be clear for many, many years to come. Speculation is, of course, easy as to possible reasons for the sudden transformation from the sub-clinical state to the clinically overt state of coronary disease. For example, the occurrence of thrombosis superimposed upon an arteriosclerotic area occurring over a period of hours and days can effect this transformation The occurrence of intimal hemorrhage into an atheromatous plaque and the changes attendant upon this can suddenly decrease blood supply critically to a region of the myocardium and produce clinical manifestations. In addition, physiologic factors operating in an individual with narrowed coronary arteries can conceivably be immedi-

ate provoking factors. The extent to which such factors as functional vascular spasm are operative is not clear but one should not rule out their possible importance. One issue must remain uppermost in the mind of the physician dealing with the problem of coronary heart disease in a preventive manner, namely, that with increase in the degree of arteriosclerotic narrowing, the risk of a clinical episode rises progressively. This is so even though no date can be assigned to such an episode nor may we know what immediate factor will precipitate the clinical episode. In problems such as these it is often worthwhile to reflect upon our medical objective. In this case our objective is the prevention of *clinical* coronary heart disease While understanding of every last facet of the physio-pathology of the evolution of coronary heart disease is a most desirable and laudable aim, this should never be allowed to interfere with efforts to reduce mortality as soon as possible whether or not the entire physio-pathology is understood The entire body of evidence on this subject would indicate that if coronary arteriosclerosis could be minimized, the incidence of and mortality from, clinical coronary heart disease would also be markedly reduced This is the essential issue here That confusion on this issue is rife in high places can best be illustrated by citing certain important studies which have attempted to cast doubt on the importance of coronary arteriosclerosis for clinical coronary heart disease. In one such study, Morris[16] has obtained data from pathological records in one large London hospital where he felt the pathological grading scheme was sufficiently similar throughout a period of 40 years to enable him to estimate whether coronary arteriosclerosis exhibited a rising trend, a falling trend, and or no change over this time period His finding in the material at his disposal from autopsy records was that coronary arteriosclerosis appears to have decreased in average degree over this 40 year span in England However, during that same span of years the vital statistics for England showed that there appeared to exist a real and striking increase in the incidence of clinical coronary heart disease and in mortality therefrom, even after correction for medical awareness of the disease and for improvement in diagnostic methods. When such a situation arises there are several

possibilities that must come into consideration. But one point, both of philosophical and scientific consequence, must first be emphasized. Whatever possibilities are invoked to explain the *paradoxical findings, they can hardly be correct if they flout* directly other existing well-established, observational data. At any time the existing *interpretation* of solidly-established observational data may require revision, even radical revision, but new facts brought to light on an issue cannot negate *facts* which have also been proven to be as solidly established. Some of the possible explanations of the observations of Morris concerning the apparently opposite trends in coronary arteriosclerosis in England and those in clinical coronary heart disease mortality are the following:

First: Is the pathological grading that has been used *really on a constant basis, such that one can use the reports of patholo*gists of even one hospital over a 40 year period for this type of analysis?

Second: Is the clinical material of the Guy's Hospital on which these conclusions are based really representative of the trends in the British population-at-large? With respect to this issue one might appreciate better assurance of the representative character of such hospital material. Physicians are well aware that numerous factors, even some over and above the type of illness which results in hospitalization of particular types of patients can change markedly from one decade to the next Indeed, they can even change from one year to the next, depending upon the introduction of new therapeutic and diagnostic tools The issue of comparability of hospital material over a 40 year period in a particular London hospital is a real and major one

Third: One may assume that the possible objections inherent in the first and second questions raised above are not valid and that *the data are as they seem to be. Then the problem* can be stated, "Are these the only data we have on this subject or are there other?" In the text above are very crucial solidly-established experimental data relating coronary arteriosclerosis to clinical coronary heart disease. Hence, we are not operating in a vacuum with respect to this problem, for we have excellent direct evidence that coronary arteriosclerosis is indeed related to

clinical coronary heart disease. No data accumulated by Morris or by others concerning arteriosclerosis trends over 40 years in London hospitals or coronary heart disease mortality in Britain over that same time period can possibly negate these well established relationships If the observations detailed by Morris are truly correct as they stand, there must be some rational way to bring them into harmony with the known, well-confirmed relationship of coronary arteriosclerosis and clinical coronary heart disease. We know well that we do not understand all the factors that convert a sub-clinical case of coronary arteriosclerosis into a case of clinical coronary heart disease This has just been alluded to repeatedly. Therefore, it would be very pertinent for us to inquire whether one or more of the factors that determine the conversion of coronary arteriosclerosis at the sub-clinical level into clinical coronary heart disease might not have undergone alteration in this 40 year period in England and thus be responsible for the trends observed Indeed, with this approach one might hope that the resolution of this apparent paradox would add additional understanding to the entire problem of coronary heart disease rather than serve merely to confuse the issues. For some reason the type of data uncovered by Morris has been used by some authors and some so-called authorities on coronary disease as evidence refuting completely a host of other relationships, such as the relationship of pathologic to clinical findings, such as the biochemical relationship of blood lipids with coronary heart disease, and still others These last mentioned relationships can in no way be contested by the type of evidence which Morris has presented, since the relationships stand on their own merits. It is indeed discouraging with respect to the progress in understanding disease that data such as those of Morris are misinterpreted and misused.

Other aspects of the relationship of coronary arteriosclerosis with clinical coronary heart disease have been equally misunderstood and misused with the result of adding confusion. A cardinal one that deserves discussion is that of the relationship between coronary artery disease in the male and the female of the human species, both with respect to the pathological features of coronary arteriosclerosis and with respect to the occurrence of

clinical coronary heart disease. The best available data indicate that the following is true for young men and young women, for *example, in the 30-39* year age decade: (1) there is, on the average, a greater degree of involvement of the coronary arteries with artriosclerotic narrowing in the men of this age group than there is in the women. (2) There is a much greater incidence of the occurrence of clinical coronary heart disease in men of this age group than in women. The exact extent to which the incidence in men exceeds that in women has been estimated to be anywhere from two-fold to twenty-fold, depending upon the authority quoted. Many of the authoritative comments on this subject are based upon material with a variety of biasses built in and hence can be disregarded entirely. It does appear however from vital statistics information that probably the correct order of magnitude of this factor of difference is about 4 or 5, that is, *men in this age decade have about 4 or 5 times as great an* incidence of clinical coronary heart disease and death therefrom as do women in this same age decade. On the other hand, the difference in the average degree of coronary arteriosclerosis between men and women of this age decade is by no means a 4 or 5-fold difference. It is a very much smaller difference. Some authorities have concluded that since the incidence of clinical coronary heart disease is about 4 or 5 times as great in the male as it is in the female but since the difference in degree of coronary arteriosclerosis *is very much less than this, there must exist* some reason why males are so much more susceptible to coronary heart disease than females, other than the factor of coronary arteriosclerosis. This type of argument is based on the *assumption* that if the clinical incidence of coronary heart disease is 5 times as great, the amount of arteriosclerosis must necessarily be 5 times as great in men than in women. A search of any of the elements of simple logic, a search of the literature, or any other available source will reveal no evidence whatever for the expectation that the difference in degree of coronary artriosclerosis between men and women must be 4 or 5 fold if the difference in clinical disease incidence is 4 or 5 fold No one has ever shown that these two related phenomena must necessarily be associated by a *straight-line relationship.* Indeed a variety of

biological phenomena, physical phenomena, and others are known not to be related in this linear way. A simple analogy would be that between the radius of a circle and the area of a circle. If the radius of a circle is doubled, the area is increased four-fold. It is highly unlikely that anyone measuring the area of circles of these two radii would express surprise that the area of the circle drawn from a radius twice as large as that of the first circle is found to be four times as much instead of two times as much Why surprise is expressed concerning the absence of a linear relationship of coronary arteriosclerosis with clinical coronary heart disease is not at all clear, except insofar as it is a manifestation of loose scientific thinking. It should occasion no surprise if the final evolution of the facts would indicate that a *ten per cent increase* in degree of arteriosclerosis above a particular value might result in a two-fold, four-fold, or even six-fold increase in the risk rate of an attack of clinical coronary heart disease This may very well turn out to be the case. Such variables need not be associated in a straight line relationship. Were this simply a matter of erroneous thinking with no consequences, one would hardly need to labor the point further. But the absence of the *straight-line* relationship between coronary arteriosclerosis and clinical coronary heart disease incidence has led some persons to state that the two phenomena must not be related at all, although all the evidence clearly proves that they are Also, and perhaps more damaging, it has led to the concept that since coronary arteriosclerosis is not adequate to explain the difference in incidence of clinical coronary heart disease between the male and female, it is necessary to look for some other factor of explanation As a result of such erroneously-based thinking, vast research projects can be initiated to uncover this hypothetical other factor which it is deemed necessary to discover to account for the male-female difference. It is not the intent here to state that no other factor could possibly exist, but rather to state very clearly and unequivocally that if fallacious reasoning leads to a search for some other factor presumed to be necessary, then such a search may very well be a wild goose chase leading to a non-existent pot of gold at the end of the rainbow.

There is another major area where misunderstanding of

the relationship between coronary arteriosclerosis and clinical coronary heart disease has delayed adequate progress with respect to the practical aspects of management of this disease. It is a very well-known fact to every physician that no method exists at the present time for an anatomical or microscopic examination of the coronary arteries during life to determine the exact degree to which they have been narrowed by arteriosclerosis. Nor does there exist any other technique which will enable one to assess the exact degree of such arteriosclerosis. For inexplicable reasons, statements repeatedly appear in the medical literature to the effect that since no method exists for measuring the degree of coronary arteriosclerosis during life, there is nothing that can be done with the problem of *clinical* coronary heart disease until such measurements are available No scientific evidence can be marshalled to support such a statement. If certain biochemical and physiologic variables *can be quantitatively related to the* incidence of clinical coronary heart disease, our inability to measure the degree of coronary arteriosclerosis in life simply has nothing whatever to do with prosecution of any of the leads that arise out of the measured relationship between the biochemical and physiologic variables and the phenomenon of clinical coronary heart disease. This important issue can be further illustrated by taking an extreme point of view. Let us assume (even though the assumption is false) that arteriosclerosis of the coronary arteries had nothing whatever to do with clinical coronary heart disease. There still would exist every reason to go forward rapidly with the study of bio-chemical and physiological variables in relation to the clinical entity, even without knowing the underlying pathology at all This is not to say that knowledge of the underlying pathology and the relationship of bio-chemistry to the pathology as well as to the clinical entity is not desirable. Of course it is an ultimate goal sought by all students of this disease. An excellent illustration of the danger of impediment to practical progress with management of coronary heart disease arising out of the erroneous impression that we must wait for a method of measurement of coronary arteriosclerosis during life is available in the field of the relationship of blood lipids with coronary arteriosclerosis and clinical coronary heart disease This

relationship itself will be elaborated on in detail in subsequent chapters. At this point it is sufficient to state that a strong relationship exists between blood lipids, in the form of lipoproteins, and clinical coronary heart disease.

Those who argue the immediate need to be able to measure the exact degree of coronary arteriosclerosis in life say, "Since the blood lipids operate via an effect on degree of coronary arteriosclerosis, and since we cannot measure exactly how much coronary arteriosclerosis there is in life, how can we possibly apply the blood lipid findings clinically?" The answer to this is that the blood lipid findings have been developed in relationship with *clinical* coronary heart disease. They do not rely in any way, for support, upon any findings having *to do with coronary arteriosclerosis.* Neither is the utility of this relationship in the practical management of prevention and treatment of clinical coronary heart disease in any way dependent upon a relationship of the blood lipids with coronary arteriosclerosis or upon any hypotheses concerning such a relationship. It is true that most workers who have studied this problem feel the evidence is extremely strong that the relationship of blood lipids with clinical coronary heart disease does arise via the intermediacy of coronary arteriosclerosis, but this is in no way necessary. Should it turn out in the future that the blood lipids are in *no* way related to coronary arteriosclerosis, the well-established relationship with clinical coronary heart disease would be just as useful and just as applicable in the problem of prevention and management of coronary heart disease. Ultimately of course one would like to know the interrelationship of all these measures and entities, but it is very important not to confuse *supposed* dependency upon one unmeasurable variable with the ability to go ahead with the problem at the clinical level. Therefore, the inability to measure degree of coronary arteriosclerosis in the living person need not in any way be a stumbling block to progress with the practical problem of prevention or treatment of clinical coronary heart disease. It is in an area such as this that it is extremely important to differentiate clearly what is meant in discussing coronary arteriosclerosis, and what is meant in discussing clinical coronary heart disease

From the point of view of the physician interested in trying to prevent clinical heart disease, from the point of view of the intelligent layman who would like to avoid coronary heart disease, interest centers in the *clinical* entity of coronary heart disease, in manifestations such as myocardial infarction, angina pectoris, arrhythmias, heart failure, and death. The interest is not primarily in the pathological process underlying such clinical states. To be sure, where understanding of the pathology could assist with the management of the problem at the clinical level, such understanding is greatly to be welcomed. However, since the essence of the problem at the practising physician's level is clinical coronary heart disease rather than pathology, it is the intention of the author of this book to develop completely in the ensuing chapters the concepts of interest for clinical coronary heart disease without any *dependence* whatever upon concepts of coronary arteriosclerosis. Where it is felt that coronary arteriosclerosis represents the mechanism by which a given effect is mediated, comments will be made to so indicate, but in no case will the development of the ideas and the application of such ideas be in any way dependent either upon facts or concepts concerning coronary arteriosclerosis. Rather, the intent is to develop for the physician reader what we know about the evolution of coronary heart disease as a clinical entity, what can be done about its advance prediction, and what can be done about its prevention and management, without any dependence upon its inter-relationship with coronary arteriosclerosis.

Chapter II

IDENTIFICATION OF FACTORS IN THE DEVELOPMENT OF CORONARY HEART DISEASE

THE SUB CLINICAL phase of coronary heart disease is that upon which major interest must center for real effectiveness in the prevention of the clinical disease *Prevention* of clinical coronary heart disease appears to have more attractive prospects than does treatment of acute clinical episodes when they arise By the very nature of the statement that coronary heart disease is sub-clinical during that period when its recognition is most urgent the inference is made that it will be necessary to develop some means of identification for *individuals* which will determine the status with respect to sub-clinical coronary heart disease. Stated alternatively, an endeavor is necessary to develop variables that can be measured which will provide some way of rating a person on a scale of risk with respect to his future prospects of evolving from the sub-clinical phase into the phase which must be avoided, namely, the phase of clinically manifest coronary heart disease. In such an endeavor one would be perfectly justified in considering any possible measurement that can be made in people, where the term might refer to measurements in the area of anatomy, of physiology, of biochemistry, of psyche, of family traits, of environment, or even still other areas It could not be predicted in advance in a totally new problem from which of these areas the significant information might arise If no information is available on this problem, one can simply screen measurement after measurement to determine whether or not any provide information concerning either the rate at which sub-clinical coronary heart disease is developing or its total extent. Quite obviously such a screening procedure could be extremely lengthy before

any variables of consequence are uncovered. *Unfortunately this* may be necessary in certain problems. In others there exist some available clues suggesting profitable directions of investigation. *At times such clues may have* arisen from animal experimentation. At other times they may have arisen through the practical clinical experience which has been accumulated over a period of years and suggests that one or another factor might be of importance. In the absence of either of these sources of possible leads, to avoid the massive screening procedure one might, from a knowledge of the pathology of a disease or from some wholly other facet, such as the inter-relationship between two diseases, get some idea of a profitable area in which to seek clues rather than to screen every possible area.

It is worth comment here upon the nature of measurements *that can be made. Measurements fall into various categories* depending upon the precision and accuracy with which they can be made. For example, with respect to the height of a man, one could measure this quite accurately and there would be no reason not to do so. On the other hand, with respect to some other factors characterizing an individual, one might be quite satisfied to be able to grade individuals into four classes, such as zero, plus one, plus two, plus three, and plus four There is nothing wrong with either type of measurement It is self-evident that where a measurement can be refined, it will in general be more useful in assessment of a trait of interest. However under certain circumstances, where a particular measurement is quite variable in an individual from day to day, or hour to hour, it would hardly be worthwhile expending too great an effort in obtaining *great precision on any single measurement, since such precision is* not warranted because of the variation with time A pre-requisite of any feature to be measured in individuals is that the feature be different in extent in those persons developing sub-clinical coronary heart disease at a high rate compared with those developing the disease at a moderate rate and different to an even greater extent from those developing the disease at a low rate It does not matter whether the measurement is *lower* in those developing the disease more rapidly than in those not developing the disease rapidly or whether it is *higher* In either event the

measurement will be useful for the present purposes. Next, it is essential that the measurement which is different for those developing coronary heart disease rapidly from those developing it at a lesser rate must be different *early enough* in the sub-clinical phase of the disease to be useful. This requirement deserves an illustration For example, if there were a measurement related to coronary heart disease that became abnormally high or abnormally low in the couple of hours or couple of days preceding a myocardial infarction, such a measurement would be of very little use with respect to minimizing the rate of development of sub-clinical coronary heart disease, which goes on for a period of years and decades. To be really useful the measurement must be abnormal early in the period of sub-clinical development of the disease, which means it must characterize the individual years, if possible, before the occurrence of a clinical manifestation of coronary heart disease, such as myocardial infarction

Another very important feature to be determined for each such measurement is the extent to which that measurement provides new, additional information concerning the problem at hand, in this case the rate of development of sub-clinical coronary heart disease It is entirely possible that in approaching a problem such as coronary heart disease one might find that not only is there one measurement of importance, but there are as many as five or more measurements that can be shown to have some relationship to the rate at which sub-clinical coronary heart disease is developing In the event that multiple measurements seem valid, it is of prime importance to determine whether or not all the measurements provide what may be called *independent*, or truly new, information If each measurement does provide independent information, then it is necessary to measure each in order to obtain the best assessment of the rating of a particular person with respect to sub-clinical coronary heart disease If the measurements do not all provide independent information, then the measurement of any which do not provide *independent* information is superfluous, confusing, and a waste of time Let us consider a specific illustration concerning this feature of independence utilizing some factors for which evi-

dence exists of a relationship with the rate of development of sub-clinical coronary heart disease. These are the blood lipid level and a family history of early clinical coronary heart disease. Do these two factors provide independent information that can be used to assess a person's status with respect to coronary heart disease at the sub-clinical level? Assume that family history of coronary heart disease can be rated on a measuring scale from zero through plus 4, depending upon the frequency of occurrence of early coronary heart disease in parents and other relatives of the individual. It is known (to be developed in detail later) that blood lipid levels are related to the rate of development of sub-clinical coronary heart disease, the higher the blood lipid level, the greater the rate of development of sub-clinical coronary heart disease. In the absence of other information it is possible that the availability both of the family history rating and the blood lipid level may provide much more information than either one alone. However, it is *not necessarily* true that availability of both types of measurement allows a better assessment of the heart disease risk in an individual under study. In order for the two types of measurement to provide more information than either one alone, they must provide independent information, in other words, information concerning factors in development of coronary heart disease that are at least in part really basically different from each other. It might be imagined, for example, that a family history of early coronary heart disease could operate in one of several possible ways, such as inheritance of an anatomically peculiar coronary vascular tree that either favors poor nutrition of the heart muscle or predisposes to narrowing of the arteries by some mechanism, or inheritance of a variety of other possible anatomical or physiologic features affecting the coronary arteries or the heart itself. On the other hand, the unfavorable family history might conceivably reflect a predisposition, on a hereditary or familial basis, to the development of elevated blood lipid levels. It should be evident that, if the family history operates only by influencing the chance that the person would have an elevated blood lipid level, the family history is then providing nothing additional to the information directly available in a blood lipid measurement. Indeed, under such circum-

stances, the family history would at best be providing far more crude information concerning the blood lipid levels than blood lipid measurement itself. In such a case one would consider that the family history provides no independent information and hence that a rating on a family history basis would contribute nothing new if the blood lipid levels are available. On the other hand if it should turn out that the family history really operates via some mechanism such as inheritance of a poor coronary vascular tree anatomically, then the situation is an entirely different one. In this event, the family history does provide additional, independent information and hence an individual's risk of development of coronary heart disease is much better assessed if both the family history and blood lipid measurements are available than with either measurement alone. Another way of presenting the problem of independence of information would be along these lines. Assume that several factors were measurable and proven to be associated with the development of coronary heart disease. Assume further that two individuals had the same value of each such factor If now a new measure becomes available, and the two individuals differ on this measurement, then is the risk of coronary heart disease higher in one of the individuals than the other? If the risk is higher, the new measure does provide independent information and should definitely be added to the battery of evaluation tests. This is essentially the scientific basis for testing independence of information provided by measurements There exist excellent statistical methods for checking the issue of independence, such methods being based in essence upon the procedure of making all but one factor out of a set of factors equal and then testing for the association of the remaining single factor with the disease in question When by such a careful statistical test the one factor still seems related to coronary heart disease, it can be inferred that statistical independence has been demonstrated Such demonstrations of statistical independence, or demonstrated Such demonstration of statistical independence, or respect to coronary heart disease is very far from an academic matter First of all, it is of tremendous importance with respect to guiding further research efforts with respect to the disease. Second, at the practical clinical level it can help avoid duplication

of effort and of tests and indeed can help avoid erroneous and serious mis-diagnosis and mis-prognosis of the future of some individuals. Thus, returning to the illustration of family history and blood lipids, let us assume that by the statistical test methods referred to above it has been demonstrated that the blood lipids are important but that the family history is of importance only because, on *the average, the blood lipids are higher in those families* where coronary heart disease has occurred excessively. In this case there is no independent information in the family history. Now, if a clinician dealing with a particular patient does not realize this fact, he can make errors in either of two directions. First, in a patient whose blood lipid status and whose family history are known, and in whom the blood lipid status is excellent but the family history is poor, this physician, not realizing the lack of independent information in the family history, might erroneously be concerned about the unfavorable family history. The correct point of view in such a situation is that, even though *on the average the blood lipids may be worse in persons with a* bad family history of coronary heart disease, this particular patient seems to have escaped the blood lipid defect and need have no fear whatever concerning the poor family history of coronary heart disease with respect to his own outlook for development of this disease. The error that can be committed on the other side occurs in the case of a person who has an excellent family history of longevity and freedom from coronary heart disease but where the person has extremely high blood lipid values The extremely high blood lipid values would indicate a high risk of future clinical coronary heart disease and a high rate of development of *the entity of sub-clinical coronary heart disease* The prognosis is therefore unfavorable If the physician assumes in such a case that the patient has nothing to fear because he has such an excellent family history of freedom from coronary heart disease, he would be giving the patient a very false sense of security unjustified by the facts This might even prevent the patient from taking necessary measures which would reduce his *high risk of future* coronary heart disease. These illustrations are presented primarily to point up the intense practical clinical importance of knowing whether or not the various factors meas-

ured truly provide information of independent character. There is one special situation that must be considered before too casual a dismissal of the independent importance of a particular factor with respect to coronary heart disease. A particular factor that is known to be associated with coronary heart disease may make its effects manifest at one period of life whereas it does not do so at some other period in life. Let us return again to the illustration concerning blood lipids and family history of coronary heart disease. In testing for independence of family history of coronary heart disease and blood lipids, one would apply the types of technique discussed above. However, the possibility has to be considered in this situation that the nature of the familial factor is such that it makes itself manifest, for example, at some relatively later period in life than early adulthood One might consider the possibility, that a poor family history *is associated* with a predisposition to poor blood lipid control, but that this predisposition does not become *manifest* in the average person until 35 or 40 years of age. If an individual at 30 years of age is under consideration and if his blood lipids are found *to be* favorable but his family *history* poor, the finding of the favorable blood lipid pattern at age 30 years *would* lead, by too casual dismissal of the family history, to the concept that family history is unimportant for this individual. However if the familial predisposition is of a type becoming manifest between 35 and 40 years of age, the family history should not be dismissed. Instead in this type of individual with favorable blood lipids at 30 years of age, the family history should put the physician on notice that the future blood lipid status of this patient should be watched In this hypothetical illustration, though the family history is operating via an effect upon blood lipids, it is providing independent information in that it tells us that the blood lipids may become abnormal *in this* person at some later time in life whereas this might not be the case in the population-at-large without this particular familial predisposition. This might be regarded as an illustration of *semi-independent* information, and hence information that should *not* be disregarded Probably this type of situation arises relatively infrequently Nevertheless we know that it can arise and should be borne in mind in evalua-

tion of the approach to factors involved in a disease such as coronary heart disease.

In summary our goal is to identify each and every factor, if there are indeed multiple factors, which provide independent *information concerning the outlook for the development of sub-*clinical and ultimate clinical coronary heart disease. For if these independent factors can be identified, we can make the best *composite assessment* of a person's status and further can utilize the possibility of a multi-faceted approach to prevention of heart disease in an individual. And the possibility of a multi-faceted approach needs to be considered. If there is *only one* factor involved, then there is no indication for a multi-faceted approach. On the other hand, if multiple independent factors really do exist, they must of course all be given attention. There may exist a difference in the ease with which one factor or another can be brought under control and it would certainly accrue to the patient's benefit to control those factors readily controllable than not to manage any of them effectively Of course, where multiple factors exist, control of all can be anticipated to produce the best clinical results in reduction of risk of heart disease.

The entire issue of independence of factors involved in the development of coronary heart disease is of great pertinence to the research worker as well as to the practising clinician. From clinical evidence, from epidemiologic studies, from endocrine studies, and from a variety of other sources new information possibly pertinent for the problem of coronary heart disease has arisen and will arise in the future. It is urgent that when such new information arises, the first question to be asked is, "Does this really provide *new*, independent information in terms of factors that are related to the development of clinical coronary heart disease?" This does not infer that the information itself is not new, but rather the question is being raised here as to whether the information is but another reflection of some factor which we already know about and concerning which cognizance is already taken. As an illustration, it may be assumed that new research suggests that the level of a particular hormone is either *lower* or higher in those individuals developing sub-clinical coronary heart disease at an excessive rate Assuming that this find-

ing had never been made before, it is obviously a "new" finding. Indeed it may be a finding of tremendous importance in our understanding of the disease as well as in our handling of it, but it is of prime urgency to know how this hormone level operates. For example, if the particular hormone under consideration operates as one factor in the control of the level of blood lipids, it is vital that this be realized. For there would be no virtue in attempting to alter that hormone level if the particular patient already has favorable blood lipid values. In this type of situation the purpose of an effort to alter the level of this hormone would be only to attempt to achieve an improvement of the blood lipid level This in no way minimizes the importance of the particular hormone, but it may save the patient and physician needless effort to alter something of no consequence of and for itself If for example one already were able to alter the blood lipid level very favorably by simple methods not involving this particular hormone, it would follow that there is no additional benefit conferred upon the patient by the alteration of the particular hormone system for itself In the problem of coronary heart disease as with other problems of this type in medicine, we must endeavor to achieve a reduction to simplest terms consistent with the reality of the situation If the simplest terms involve the consideration of ten separate independent factors, we have no choice but to deal with all ten On the other hand if the simplest terms involve one or two factors, it is confusing and a waste of effort to retain eight or nine additional duplicative factors that truly have no independent position with respect to acceleration of the disease process under consideration.

THE IDENTIFICATION OF INDEPENDENT FACTORS ASSOCIATED WITH THE DEVELOPMENT OF SUB-CLINICAL CORONARY HEART DISEASE

It was stated above that in a new problem one could approach the search for factors related to the development of the disease by screening processes, screening every possible anatomical, physiological, and biochemical value, or one could, alternatively, utilize leads that arise through a variety of sources. In the case of coro-

nary heart disease we have been abundantly presented with leads suggesting factors to be investigated. It may be pertinent at this point to list some of the numerous leads that investigators of the problem of coronary heart disease have had available to them and the sources from which these leads came. It is of interest to remark, however, that the entire list of leads have so far produced only two factors that appear to be independent ones related to the acceleration of development of coronary heart disease at the sub-clinical level. At the present time all the others seem very likely to be related to one or another or to both of these two factors.

These leads are listed below:

(1) The greater frequency of occurrence of episodes of clinical coronary heart disease with increasing chronological age.

(2) The greater frequency of occurrence of clinical coronary heart disease in the male of the human species as compared with the female especially at relatively young ages.

(3) The occurrence of excessive and premature coronary heart disease in certain families characterized by blood lipid disturbance.

(4) The occurrence of premature coronary heart disease in diabetics at least in the pre-insulin era and the transition era.

(5) The similarity of the blood lipids to those in the arteriosclerotic plaques of the coronary artery.

(6) The induction of arteriosclerosis by cholesterol feeding in a variety of animals

(7) The difference in geographic incidence of coronary heart disease as determined by epidemiologic studies

(8) The implication of the diet of certain peoples in development of coronary heart disease.

(9) The change in incidence of coronary heart disease during privation, as in war years and post-war periods.

(10) The frequent association of coronary heart disease with hypertensive disease

(11) The occurrence of excessive arteriosclerosis in areas of the vascular tree subjected to excessive pressure.

(12) The excessive incidence of coronary heart disease in cigarette smokers.

(13) The excessive heart disease mortality in overweight persons.

(14) The widespread opinion that a family history of excessive vascular disease is a predisposing factor to coronary heart disease.

(15) The rising trends in mortality from coronary heart disease in the past half century in Western civilization.

(16) The striking relationship of xanthomatosis with coronary heart disease.

(17) The association of coronary heart disease with certain other diseases such as nephrosis and myxedema.

(18) The difference in coronary disease incidence for various occupational categories.

If coronary heart disease truly had some 15 to 20 independent factors involved in its development, the medical task of prevention and management would certainly be complicated and difficult. But 15 or 20 clues do not necessarily mean the existence of 15 to 20 independent factors in the disease. The first step is a determination of the validity of the information in the clue. Next, valid information derived from each clue must be assessed for its independence. At the present time, of all these clues and suggestions concerning coronary heart disease, *two major* factors have stood the test of careful analysis as being capable of providing valid *independent* information about the development of subclinical coronary heart disease and, of course, of ultimate clinical coronary heart disease. All the others appear to derive validity through a relationship with one or another of these two factors or with both. Therefore, the considerations immediately ahead deal with these two factors. The later chapters of this book will deal with the relationship of the other clues and suggestions to these two factors. It is not meant that the two factors to be described here are the only two that will ever be discovered to have independent status, or that other factors are either not valid or of importance. Validity and importance are issues of a different type from that of independence of information.

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highly recommended and while the findings derived therefrom often provide excellent leads for study of the human problem, the ultimate evidence with respect to blood lipids or any other factor must be derived *in the human population* directly. We must remain cognizant of the marked differences in the various animal species and of the possibility that what is important for one animal species may not hold for another. Indeed what may be important for *several* lower animal species may not hold for the human. Therefore while no thought should be given to the idea of deprecating results on coronary disease in the chicken, the rabbit, or the dog, it is still true that our interest is coronary heart disease in the human. Therefore any findings that must go into the day to day practice of clinical medicine in the effort to prevent coronary heart disease must have been proven valid for the human. This generalization holds for blood lipids or any other factor of interest.

How is the problem approached of demonstrating whether or not a factor such as the blood lipid level is associated with the development of coronary heart disease? Secondly, and beyond the question of association, is the measurement of blood lipids of practical clinical utility in determination of the rate of progression of sub-clinical coronary heart disease and hence in prediction of the most likely candidates for future clinically-manifest coronary disease? Even though some of the clues that lead to the study of blood lipids arise out of pathological considerations of coronary arteriosclerosis, the development of the evidence concerning blood lipids in clinical heart disease can and will be made wholly independent of any consideration of pathology. The reason for doing this was adequately explained in the previous chapter. It is not that the pathology is unimportant, it is not that we cannot learn from pathology, but inasmuch as our direct and practical concern is with the entity at the clinical level, it is important that any case made for blood lipids and their relationship with coronary heart disease be wholly independent of any of the pathological considerations. In this way numerous questions, criticisms, and doubts can be resolved immediately, since there is no dependence whatever on any pre-conceived

THE GENERAL PRINCIPLES INVOLVED IN TESTING FACTORS FOR RELATIONSHIP WITH CORONARY HEART DISEASE

In the evaluation of the significance of such factors as blood lipids and blood pressure in coronary heart disease, certain highly important general principles are involved, principles that can be utilized profitably in similar problems both with respect to other factors in coronary heart disease, and with respect to factors related to any disease. Such principles can be readily understood by combining their general features with a specific illustration of their practical clinical application, utilizing in this case blood lipids in coronary heart disease.

The suggestion that lipids of the blood might be associated with the development of coronary heart disease is a very old one, which comes to our attention from a variety of types of evidence. Listed previously were several of the areas of suggestion that the lipids of the blood might be important. Among these are experimental induction of an arteriosclerotic lesion in animals by the feeding of cholesterol, the finding that the lipids in the arteriosclerotic lesion are closely similar to the lipids of the blood, the excessive incidence of coronary heart disease in families with xanthomatosis or with blood lipid disturbances, and the excessive incidence of coronary heart disease in diabetics, at least in the pre-insulin era at which time many diabetics were frequently characterized by markedly elevated blood lipids. These are all but clues, falling short of provision of the direct answer concerning the role of blood lipids in the development of coronary heart disease in the population-at-large. It is precisely this group with whom we are concerned, since the overwhelming number of cases of coronary heart disease arise out of the population-at-large. If the blood lipids were of consequence only for relatively special categories such as the individuals with xanthomatosis, they would hardly be of much merit or significance with respect to the real problem of coronary heart disease, which goes vastly beyond that of coronary disease in a highly special group of individuals such as xanthomatotic subjects. Furthermore, while the use of experimental animals, such as the rabbit, the chicken, the dog, the rat, or the monkey for studies of arteriosclerosis is to be

such factors as age, sex, etc.) but free of evidence of clinical coronary heart disease. The presumption here is that, while coronary heart disease is developing to a greater or lesser extent in those free of *overt* clinical disease, on the average these individuals have a lesser degree of the disease and have been developing it at a slower rate than those of the same sex and age group who have already presented clinical signs and symptoms of coronary heart disease. This presumption is actually closer to a definition, for if *clinical* coronary disease is the problem at hand, it is obvious that those who manifest it have more of it than those who do not. This represents one valid manner of approaching such a problem. However, there do exist certain fundamental objections to this approach alone. First the measurements in those persons with clinically-manifest coronary disease are being made *after* overt signs and symptoms are present. Therefore it is impossible to know at what point in such a person's life any proven abnormality in blood lipids had appeared. For utility in the direction of the ultimate objective of early interruption of sub-clinical coronary disease it is essential that the blood lipid factors under study be abnormal early in the *sub-clinical phase.* The study of persons with manifest coronary heart disease does not provide any way of knowing whether a factor (such as blood lipids) became abnormal shortly before clinical signs or had been abnormal many years before. Indeed there is even a more dangerous possibility namely that the lipid abnormality appeared *after* the onset of clinical signs and symptoms either spontaneously or as a *result* of the clinical episode. If this possibility were a reality, the information would be useless for the purpose we have in mind, namely using the measurement of such factors to evaluate and rank people during the sub-clinical phase of coronary heart disease. *Even* if the abnormality of the measurement appeared a very short time *before* clinical signs and symptoms, the usefulness of the information would be extremely limited for purposes of identification of high-risk candidates and for the institution of preventive measures. Why, then, should one consider at all the measurement of some variable such as blood lipids in subjects with *overt* coronary disease in the effort to evaluate possible factors involved in its development? The

notions concerning the interrelationship of coronary arteriosclerosis with sub-clinical and clinical coronary heart disease.

Thus, the problem at hand is an evaluation of the blood lipid factor in the evolution of coronary heart disease as a clinical entity, rather than as a pathological entity. However, our concern is mainly with the *sub-clinical phase* of the clinical entity. The type of study needed must bypass any pathology considerations and go directly to possible relationships between blood lipids and clinical development of coronary heart disease, either in its sub-*clinical or manifest phases. If blood lipids do represent a factor* in the development of clinical coronary heart disease, there must be *some* difference between the blood lipids of those humans with coronary heart disease and those humans without coronary heart disease. Or, if we regard coronary heart disease as a graded phenomenon, rather than a "yes or no" phenomenon, then there must be a progressive difference in the blood lipids as one passes from individuals with a low degree, or rate of development, of coronary heart disease to those with a higher degree, or rate of development of this disease. It is of no moment whether the blood lipids be higher with increasing degree of disease, or lower with increasing degree of disease, but there must be a *difference* in blood lipids in passing from those persons with less disease to those with more disease, or those developing disease slowly in *contrast with those developing disease rapidly*

THE CHOICE OF SUBJECTS FOR STUDY

Evaluation of the relationships of blood lipids with coronary heart disease requires availability of some way to grade the degree of disease or the rate of development in the subjects studied. But, as was mentioned earlier, no direct method exists to measure the degree, or the rate of development, of sub-clinical coronary disease, which is precisely what we would most like to measure. Two alternative choices suggest themselves

(*a*) *Comparison of blood lipids in a group of subjects with* documented manifest clinical coronary heart disease (in the form of angina pectoris or myocardial infarction) with the blood lipids in a group of *subjects otherwise comparable (with respect to*

ment of coronary disease could be identified by the blood lipid measurement at least 5 to 10 years before the transition to clinically overt disease. This type of evidence is precisely what is needed concerning sub-clinical coronary disease, free of the objection that the clinical episode itself may conceivably have produced the abnormal blood lipid level.

ASSOCIATION, PREDICTION, AND CAUSE AND EFFECT

When a variable, e g, blood lipid level, is measured in a disease entity such as coronary heart disease and in matched controls without overt heart disease and the mean level shows a difference between the two groups, whether higher or lower in the disease group than in the controls, it is possible to state that this variable is *associated* with the disease process. What the nature of that association is remains in any particular case to be demonstrated No clear-thinking scientist would ever claim that proof of association of a variable (such as blood lipids) with a disease (such as coronary disease) represents proof that the blood lipids are either *a* cause or *the* cause of the disease (such as coronary heart disease). But proof of association is the first step, and indeed a vast and major step forward This is an important issue, since misunderstanding of this differentiation has led some investigators to minimize the significance of proven associations between a measurement and a disease. Such investigators are prone to state, "All this proves is association, but it doesn't prove cause and effect." And with such a statement they blithely pass off as of little consequence associations of major and practical clinical importance

When an association has been proved between a measured variable and a disease, there are several possibilities that account for the association, among which are.

(a) The disease itself may cause the measured variable to be abnormal

(b) Both the disease and the measured variable may be affected by an underlying metabolic or other defect which is itself the true cause

(c) The abnormality in the measured variable may be the cause of the disease process

answer is the highly practical one that alternatives to this are very costly of time and effort and hence delay progress in understanding. The utilization of subjects with already-established clinical signs and symptoms of coronary heart disease is of great value as an *introductory* procedure to this problem, for subjects are available in great numbers, without the necessity of waiting for the clinical disease to develop in healthy persons. Because of the limitations just described (i.e., not knowing whether any blood abnormality did or did not precede the clinical event), it is imperative to supplement studies of groups with overt disease with additional long-term studies where the overt disease is permitted to develop out of a population in apparent health at their initial study. Thus, in the case of coronary heart disease, it is necessary to evaluate a variable of possible interest, such as blood lipid level, in a large sample of the population at a time when the persons involved are overtly well (which means that many are in various stages of *sub-clinical* coronary heart disease). The size of the population sample requiring study depends upon (a) the frequency with which apparently healthy people develop clinically overt coronary disease and (b) the time period over which the subjects are observed. A small sample observed over a long time period can usually yield the same information as a large sample observed for a short time period.

The value of such a study, should it reveal that those who later develop clinical coronary heart disease are either *higher* or *lower* in blood lipid level than the mean value for the population out of which they have grown, is that it has been shown that the blood lipid level is *different* for future coronary disease patients from that for the population-at-large *at a time when such persons are in the sub-clinical phase of the disease* For example, if a follow-up period averaging 1 year is utilized, then it would be known that the blood lipids are abnormal *at least* one year before the clinically overt disease is manifested If a follow-up period of 5 or 10 years is the average time period for the cases of coronary disease to grow out of the population, then it would be known correspondingly that the abnormality in blood lipids was present 5 to 10 years before overt symptoms and signs. Stated somewhat differently it would mean that sub-clinical develop-

ment of coronary disease could be identified by the blood lipid measurement at least 5 to 10 years before the transition to clinically overt disease This type of evidence is precisely what is needed concerning sub-clinical coronary disease, free of the objection that the clinical episode itself may conceivably have produced the abnormal blood lipid level.

ASSOCIATION, PREDICTION, AND CAUSE AND EFFECT

When a variable, e g, blood lipid level, is measured in a disease entity such as coronary heart disease and in matched controls without overt heart disease and the mean level shows a difference between the two groups, whether higher or lower in the disease group than in the controls, it is possible to state that this variable is *associated* with the disease process. What the nature of that association is remains in any particular case to be demonstrated No clear-thinking scientist would ever claim that *proof* of association of a variable (such as blood lipids) with a disease (such as coronary disease) represents proof that the blood lipids are either *a* cause or *the* cause of the disease (such as coronary heart disease) But proof of association is the first step, and indeed a vast and major step forward. This is an important issue, since misunderstanding of this differentiation has led some investigators to minimize the significance of proven associations between a measurement and a disease. Such investigators are prone to state, "All this proves is association, but it doesn't prove cause and effect" And with such a statement they blithely pass off as of little consequence associations of major and practical clinical importance.

When an association has been proved between a measured variable and a disease, there are several possibilities that account for the association, among which are·

(a) The disease itself may cause the measured variable to be abnormal

(b) Both the disease and the measured variable may be affected by an underlying metabolic or other defect which is itself the true cause

(c) The abnormality in the measured variable may be the cause of the disease process

Ofttimes direct experimental choice among these three possibilities may be difficult, or even impossible. But this need in no way be discouraging, for there are many indirect ways to solve the practical problem even though the direct proof may be lacking concerning the nature of the association.

The three possibilities mentioned above deserve illustration and consideration with respect to the problem at hand, namely coronary heart d sease.

The possibility that the disease itself is responsible for the abnormality in the measured variable in this case of blood lipids may be approached first. If one had discovered the abnormality of the variable in patients who had had a myocardial infarction, for example, it is possible to believe that the metabolic alterations attendant upon occurrence of a myocardial infarction might have themselves been responsible for the abnormality in the measured factor (e.g, blood lipids) However, this is precisely one of the reasons why one is not very satisfied with the discovery of an abnormal variable (such as blood lipids) in patients who have already manifested clinical myocardial infarction. This is also the reason for the need to do *prospective* studies where the bio-chemical measurements are made in individuals when they are in apparent health and where infarction or other clinical manifestations are then permitted to develop in a population of such individuals. The possibility would still exist even in the study of the sub-clinical disease to consider that the actual occurrence of the sub-clinical disease developing might be the cause of the abnormal lipid measurements While patients developing sub-clinical coronary disease show no evidence whatever of an illness that might be suspected to lead to metabolic aberrations, the possibility cannot be ruled out that the disease itself is the cause of the abnormal lipid levels, although it certainly would seem much less likely than would be the situation wherein patients are studied in the already clinically manifest phase of coronary disease. Since the possibility cannot be ruled out, one must consider what the implications of such a prospect are. If, for example, identification of individuals with sub-clinical coronary disease is our objective and if the blood lipid abnormality were the *result* of the sub-clinical disease, this need not matter

in any way for our purposes. The results would be just as valid for purposes of identification of individuals developing subclinical coronary heart disease *whether or not* the disease caused the lipid abnormality. However, if our purposes are other than identification alone, then it would make some difference whether the disease causes the lipid abnormality. For example, if one were interested in the possibility that correction of the lipid abnormality would have some effect upon amelioration of the disease, the prospects would be dim if the disease *caused the lipid* abnormality The only conceivable way to determine this in the absence of direct information would be to make direct tests of the concept that decreasing the degree of the lipid abnormality in any way ameliorated the disease. If such tests showed a positive result, no further need would exist to raise the question of whether the disease caused the abnormality, since the objective itself, inhibition of the disease, would have been realized. In this sense, it is entirely appropriate to allow our objective to determine our course of action rather than to wait until some indefinite future for the direct proof of whether or not the disease causes the abnormality or the abnormality is one factor which causes the disease

The second possibility is that the disease and the abnormality are both the result of some other feature, be it a metabolic abnormality or some other property, rather than that the lipid abnormality is the cause of the disease, or the disease, the cause of the lipid abnormality One could visualize, for example, that a metabolic dysfunction such as that in the liver might in some way alter blood lipids and by some wholly separate mechanism might provide an effect upon the cardiovascular system leading to coronary heart disease While such a possible mechanism is not immediately obvious, it cannot be summarily dismissed In this case one might anticipate the possibility that alteration of the blood lipid factor (even though it has been proved to be associated with the development of coronary heart disease) might not slow the rate of development of coronary disease This possibility must be considered both with respect to prevention and therapy However, two points are to be borne in mind in such a case First, with respect to *prediction* of who is developing exces-

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disease some 30 years ago, and as evidence accumulates it appears increasingly certain that his concept needs no appreciable modification

sive sub-clinical coronary heart disease, the possibility of a third factor being the cause of both the lipid abnormality and the coronary heart disease *is of no moment whatever.* For, all that is needed to achieve the requisite *predictive* information is the existence of a *relationship* between the blood lipids and the development of sub-clinical coronary heart disease, whatever be the cause of either one of them. Second, the hypothesis of a third cause is simply an hypothesis, based upon no facts. Unless *some* facts develop in its favor, it is difficult to see why this more complicated hypothesis is chosen by some individuals rather than the simplest one *directly* relating the abnormality of the blood lipids with the development of coronary heart disease. When one chooses the simplest hypothesis, this does not mean that one insists on the correctness of it, but rather that it *is* the simplest hypothesis and therefore deserves careful and intense evaluation to determine its truth or falsity. The actual practical evaluation of such an hypothesis will of itself provide the best determination of correctness. Certainly this is an approach far superior to the entirely unwarranted assumption that the simplest hypothesis must be wrong Here again the practical issue is paramount If one chooses to evaluate the simplest hypothesis that possibly the blood lipids may be a *cause* of coronary heart disease and follows up the implications thereof, namely, whether lowering or altering the blood lipids will alter progression of coronary disease, one may very well achieve the tremendous clinical result which is desired, namely, prevention or minimization of coronary heart disease The practical test itself will have laid to rest much of the need for consideration of possibilities of a more complicated relationship. Until and unless this extremely important possibility has been shown to be incorrect by direct clinical test thereof, it remains the most attractive hypothesis deserving of study For, in the case of blood lipids and coronary disease, one is led to this simplest hypothesis not only by a strong set of data, namely, association between the blood lipids and sub-clinical coronary heart disease, but also by massive indirect evidence which suggests that the relationship is truly a causal one. Anitschkow[4] suggested the causal relationship between blood lipids and coronary heart

exist as such circulating in the blood stream. Thus, even such a term as 'free cholesterol" or "esterified cholesterol" is misleading since it tends to indicate or to suggest that these are two separate entities circulating *as such* in the blood. This is not the case There can be demonstrated no evidence for any significant quantity of cholesterol circulating in the blood as such, or of phospholipids circulating in the blood as such, or of triglyceride circulating in the blood as such, or of fatty acids circulating in the blood as such. Instead all of these chemical constituents which comprise the lipids of blood are substructural units, or building blocks, for a series of very large molecules that do exist as such in the blood and which have been designated as *lipoproteins*. The designation, lipoproteins, simply implies the presence of structural entities in the blood comprised in part of lipid and in part of protein The designation itself *does not* imply any specific protein or any particular lipid. Therefore whether cholesterol, cholesterol and phospholipid, or cholesterol, phospholipid, neutral fat, and fatty acid are all present in a particular lipoprotein is not the feature required to allow this definition or designation If any one of the lipid entities is associated with protein to form a macromolecular structure, such a structure would be referred to as a lipoprotein The lipoproteins are molecules of very large size, even the *smallest* lipoprotein being larger in size than a serum globulin molecule. The lipoproteins are *the* transport vehicles for the lipids in blood Many investigators have commented on nature's need to solubilize the lipids in blood through the attachment of the various lipids to protein. Whatever the merits of this type of reasoning, it can hardly add anything to the statement that lipids are transported essentially completely in the form of a series of lipoproteins The lipoproteins of blood represent not a single or a few specie (s), but rather a whole range of molecular entities from sizes approximating that of gamma globulin to tremendous sizes, such as those familiar from dark field microscopy as the chylomicrons. A compound such as cholesterol finds itself as a constituent of every single class of lipoproteins that has been analyzed. Therefore, we have immediately before us the possibility, if the various lipoproteins differ in concentration from person to person, which they do,

Chapter III

THE BLOOD LIPID FACTOR IN CORONARY HEART DISEASE

A PREREQUISITE to evaluation of the blood lipid factor in coronary heart disease is a concept of our present-day knowledge of the nature of the circulating blood lipids. Two major modalities of characterization have been applied to the blood lipids, the first being chemical and the second being largely physical in nature. Historically the chemical characterization preceded the physical characterization, primarily the result of the earlier availability of chemical techniques for analyses. There can, of course, exist no *real* conflict between such modalities of analysis nor can there be any inconsistency in the results derived therefrom, providing both types of analyses are correct. There exist, however, many good reasons to consider that the more modern physical techniques for analysis of the blood lipids may be of the greater value. For the physical techniques describe the blood lipids in a state resembling closely that in which they exist in the blood. Second, they provide a more intimate characterization and delineation of the various blood lipids of potential interest in the problem of coronary heart disease. The detailed basis for these statements will become apparent in later discussions.

Chemically, the lipids of the blood are comprised largely by cholesterol, some of it free and some of it esterified with various fatty acids, triglyceride or neutral fat, phospholipids, free fatty acids, and possibly by several other constituents at very low abundance. The first three are certainly the major constituents on the basis of abundance. The results of modern physicochemical techniques applied to the problem of the blood lipids show clearly that the chemical entities described above do not

rates even though very small molecules (such as glucose) do not. The second property of lipoproteins that makes them especially adaptable to ultracentrifugal analysis is the fact that they possess a physical density (grams/milliliter) that is considerably different from the density of the much more abundant *proteins* of blood Whereas the density of the proteins of blood is approximately 1 3 grams per milliliter, the density of the most dense lipoproteins of blood is only 1.15 and the density of other lipoproteins range downward from this value to values even below 1 gram per milliliter This means that if a solution is prepared from serum by the addition of sodium chloride or some other salt or sugar which thereby places the solution density between the density of the lipoproteins and that of the proteins, it is possible to effect a neat separation of the proteins and lipoproteins. The lipoproteins then *float* in the ultracentrifuge while the proteins *sediment* This is the first step in lipoprotein analysis of serum. Once the lipoproteins have been separated from the proteins by this method, they are available for the step known as the analytical step which utilizes a larger ultracentrifuge equipped with an optical system for determining the kinds of lipoproteins that are present and the concentrations of each type present in a serum sample It is customary in ultracentrifuge practise to refer to the speed to which any particle migrates under the effect of an intense gravitational field as its sedimentation rate, or migration rate, in "S units" The "S" stands for Svedberg and is so named in honor of The Svedberg who invented and pioneered the ultracentrifuge Thus, if one were speaking about serum albumin molecules, which migrate in an ultracentrifuge under standardized conditions with 4 arbitrary units of speed, the albumin molecules would be referred to as molecules of the 4S, or 4 Svedberg, class The *proteins*, which are more dense in general than the solutions in which they are migrating, sediment outward in the centrifugal field, or in the direction of the centrifugal field The units of migration are chosen to be positive in this direction, so albumin would have a migration rate of *plus* 4 units of speed in Svedberg units However, under the usual circumstances of lipoprotein analysis, the lipoproteins are made to undergo flotation *toward* the center of rotation, rather than

that a specified amount of cholesterol in the blood can mean very different things from one person to another. The same considerations would apply to phospholipids or to triglyceride, a specified amount of *either of these substances meaning possibly* very different things in different people. This can be restated that a specified chemical constituent (such as cholesterol) in one person may be primarily in one type or in a few types of lipoprotein, whereas in another person that same chemical compound might be distributed *primarily in other types of lipoprotein.* The intimate characterization of the lipoproteins in the blood and their measurement is at present most effectively and easily achieved by the physical technique of ultracentrifugation There is no other method which provides the detail concerning the distribution of types of lipoproteins in the blood and the measurement of the various classes that is even remotely comparable with the quality of data obtainable via the ultracentrifugal technique. That this technique will in the future be the best way of analyzing the lipoprotein distributions in blood is of course not foreseeable Should any simpler, more effective, or more critical technique be evolved, it would certainly be of great value to utilize such a newer technique for the analysis of the blood lipoproteins, although at present no such technique is in the offing. One might ask whether other techniques are available which for practical clinical purposes might serve adequately, even though for research purposes the ultracentrifugal technique is a necessity. The answer is that some of the highly practical *clinical* questions (which will be dealt with later in this book) require the ultracentrifugal analysis of the distribution of serum lipoproteins for most effective identification of the type of disorder involved and for the handling of those disorders in a medical management sense There are two properties of the lipoproteins of human blood which make the ultracentrifuge especially useful in their analysis The first property of the lipoproteins is their very large size The ultracentrifuge is an instrument which is in principle the same as an ordinary centrifuge, and hence particle size is of major consequence. With the powerful centrifugal fields available in the ultracentrifuge the lipoproteins in the blood are of large enough size to migrate at reasonable

flotation rate in S_f units, and that their concentrations can be measured in the usual clinical terms of milligrams per hundred milliliters directly from the ultracentrifugal analyses. There is one caution, however, that is important to stress. In the earliest centrifuge work lipoproteins were studied in a relatively dilute solution and their values were reported *directly* in terms of migration rates in S_f units. However, for certain purposes of precision and accuracy it became convenient to study the lipoproteins ultracentrifugally in more concentrated solutions. Under these conditions lipoproteins tend to slow themselves down in migration rate because of their being in high concentration. As a consequence all migration rates must be corrected in a standard manner before reporting of results. This correction can be very precisely applied and should be applied. There is no question of error involved in the use of concentrated solutions provided the appropriate corrections are applied. When this correction is applied, the lipoproteins are reported in terms of *Standard* S_f units, or "s_f units." The word, standard, or the superscript, zero, applied to S_f means that the worker has applied all the corrections necessary for proper analysis of ultracentrifuge diagrams. Certain workers in the field have not fully appreciated the significance of the necessity to report ultracentrifuge results in the standard flotation rate, or s_f, units and have used concentrated solutions for ultracentrifugal analyses without applying the corrections. They have reported their work directly in S_f units. Such work is neither comparable to the early work in dilute solution[13] nor is it comparable to the correct method of ultracentrifugal analysis, employing standard S_f units. Therefore the reader is urgently cautioned to view with skepticism any report of ultracentrifugal analyses of lipoproteins in disease states or in health, where concentrated solutions have been utilized and where the results are reported in uncorrected S_f units instead of the standard S_f units in which they should be reported. A case in point where erroneous clinical conclusions were reached because of failure to utilize standard flotation rates is in the work of certain laboratories reported in the so-called Cooperative Study of Lipoproteins and Atherosclerosis[14].

The lipoproteins of human blood are divided into two broad major groups, the group of largest abundance and of primary

outward in the direction of the centrifugal force. In other words since the lipoproteins are migrating in a solution more dense than themselves, they migrate inward against the direction of *centrifugal field*. In order to avoid the cumbersome use of negative units for such flotation, a unit was introduced some ten years ago known as the *Svedberg of flotation*, or "S_f unit"[11]. This means precisely the same in terms of units of speed as for the proteins, except that materials are floating instead of sedimenting. Thus, if a lipoprotein floats as fast as albumin sediments the lipoprotein is called a molecule of the 4S_f class to correspond to the nomenclature of 4S for the albumin molecule. The description of lipoproteins in terms of flotation rate in S_f units is more than just a physical measurement, since it proves convenient as an actual naming system for the various lipoproteins. Had it turned out that nature were extremely simple and there were only a few lipoprotein species present in human blood, they might have been named by such terms lipoprotein one, two, and three, or lipoprotein A, B, and C. However, the studies of human blood have *shown that there exists an entire host of lipoproteins ranging in* size from the smallest, which are approximately 200,000 in molecular weight, up to the largest which are millions of millions in molecular weight, with a great number of intermediary species *being known to exist. There just wouldn't be enough letters in* the alphabet to name them by arbitrary names Furthermore naming of the lipoproteins by the physical measurement of the number of Svedbergs of flotation of migration rate proves to be very useful, for the name means something in terms of a physical constant that can be reproduced under standard conditions by workers anywhere in the world with ultracentrifugal equipment. In all the subsequent discussions of the relationships of lipoproteins with coronary heart disease, lipoproteins will be named in terms of their migration rate in the ultracentrifuge under a set of arbitrarily defined standard conditions in S_f units The precise technical details of ultracentrifugation have been described in extenso elsewhere[12]. It is neither the purpose of this discussion nor this book to present such technical issues in detail For our present purposes it is sufficient to note that a large number of lipoproteins exist in human serum, that they are named by their

teins between any two of these dividing points The sum of concentrations of all the lipoproteins between flotation rates of s_f0 and s_f12 is referred to as the concentration of the s_f0-12 lipoprotein class. Correspondingly the sum of concentration of all the lipoproteins floating between the rates of s_f12 and s_f20 is referred to as the concentration of the s_f12-20 lipoprotein class. Similar procedures are used to determine the s_f20-100 and s_f100-400 lipoprotein classes. Most lipoprotein analyses are reported in these general bands. The question may be raised as to whether there might not be some better banding or some sub-banding that would be of importance. Such a possibility can never be ruled out, but it can be stated that, if in the future a different banding should be proved to be of greater value, an old ultracentrifugal run can be re-evaluated in terms of such new banding. At the moment there appears to be little advantage with respect to the study of a disease such as coronary heart disease of any banding beyond that which has already been described. Indeed for certain purposes the three classes, s_f12-20, s_f20-100 and s_f100-400 lipoproteins are added together and reported as the s_f12-400 lipoprotein class. This type of procedure is one of general applicability. Thus, if the concentrations of s_f20-100 and s_f100-400 lipoproteins are added, the sum of these two concentrations can be referred to as the concentration of the s_f20-400 lipoprotein class.

It is now possible to turn attention to the problem of whether or not any of the lipoproteins of human blood are associated in some way with coronary heart disease. The ultimate objective sought might be restated here, namely, a measurement which would be related in a *predictive* sense to the rate of development, or of the degree of development of sub-clinical coronary heart disease. If human blood lipoproteins are found to be associated with coronary heart disease, the first question that must be asked is, "*Which* lipoproteins are involved, the s_f0-12 class, the s_f12-20 class the s_f20-100 class, or the s_f100-400 class, or some combination of these classes?" The next question to be answered is, "If all classes or several classes of lipoproteins are involved, does the measurement of each class provide *independent* information?" It is of course possible that one class of lipoproteins may be simply a "rider," being abnormal simply because the level of this class of

interest with respect to coronary heart disease being that known as the low density lipoproteins. Such lipoproteins are all characterized by densities of 1.05 gms/milliliter or less. There are, in addition, three groups of lipoproteins which are referred to as high-density lipoproteins, all of densities 1.05 gms/milliliter or greater. The high-density lipoproteins will be referred to in a subsequent chapter under the subject of various chemical analyses in connection with prediction tests for coronary disease (Chapter XV) and will not be dealt with further at this point. The low-density lipoproteins under standard conditions, or in Standard S_f units, migrate with rates of 0 units up to some 40,000 units of speed. In the vast majority of human cases the bulk of these lipoproteins are contained within the range of speeds from 0 to 400 units. This band is also incidentally the most readily studied by ultracentrifugal procedures. Even within the region of s_f0 to s_f100 there exists a very large number of lipoprotein species. One cannot be sure, at this time, of the exact number of species that is present. If measurements were to be made of lipoproteins in relationship to coronary heart disease, the analysis of concentration of each and every lipoprotein class from s_f0 to s_f100 would be an almost insurmountable task. However, there are alternatives to measurement of each and every lipoprotein within this region from s_f0 to s_f100, alternatives which have been shown to be highly productive. One such alternative is to divide the region from s_f0 to s_f400 into several bands. The actual choice of limits of bands is somewhat arbitrary, although there appear to be some regions of logical sub-division. Such regions were chosen through large experience with ultracentrifugal analyses, which revealed that *points such as s_f12, s_f20 and s_f100 are what might be called natural* dividing points. Many humans show a minimum in their lipoprotein concentrations in these particular regions. As a result of using such dividing points, lipoproteins are characterized as those which float between the rates of s_f0 and s_f12, those which float between the rate of s_f12 and s_f20, those which float between the range of s_f20 and s_f100, and those which float with rates between s_f100 and s_f400. A convenient, practical procedure that has been utilized in over 100,000 routine ultracentrifuge analyses of human blood is to measure the sum of the concentrations of all lipopro-

ing such investigations. In such a study one is desirous of minimizing any disturbing factors extraneous to the factor of the existence of clinical coronary heart disease itself. Thus to contrast the serum lipoprotein levels in patients with clinically established coronary heart disease with persons in overt health (those without clinical manifestations of coronary heart disease), one would not like to have the patients with clinical coronary heart disease in a metabolic state unusual for them. For example, one would prefer to have patients who are on the same diet which has characterized them during the period of life before their clinical manifestation of heart disease. The possibility had existed and has now been abundantly confirmed that dietary change can of itself profoundly alter serum lipoprotein levels One would prefer that the patients be at precisely the same weight that had habitually characterized them before their episode of clinical coronary heart disease. One would prefer that they be taking no medications that they were not taking before their episode of clinical coronary heart disease Quite obviously the various clinical sources of material available for this type of study do not allow for attainment of such ideal clinical cases. For many, many years numerous physicians have had definite ideas concerning diet, weight control, and certain medications in relation to coronary heart disease, wholly apart from blood lipid considerations. Hence, patients who present with clinical coronary heart disease have necessarily received some advice and management which may alter their metabolic status. Nevertheless one can exclude cases where more than a certain amount of weight has been lost since the clinical episode, and if such exclusions are made before the lipoprotein analyses are available, there is very little possibility of biassing the material in this way. Furthermore, in the very acute phase of an episode such as myocardial infarction there is the possibility of shock and its attendant metabolic alterations which one would also want to avoid. For this reason the study of patients with clinically established coronary heart disease has been limited to those who were at least six weeks beyond the occurrence of an acute episode of myocardial infarction The acute phase has been studied in addition, but this was not part of the original program of evaluation The question of matched con-

lipoproteins may be highly correlated with the level of some other lipoprotein class that is directly involved in coronary heart disease A third major question that would arise is, "At what stage in the evolution of coronary heart disease does any association between lipoproteins and the disease first manifest itself?" In the general discussion of possible factors associated with coronary heart disease it was pointed out that if a variable becomes abnormal *after* the clinical event is manifest, but is not abnormal or unusual during *the sub-clinical stage, it would not be of especial interest for the* purposes desired. Therefore it is urgent to know how early in the evolution of the sub-clinical phase of coronary heart disease any disturbance of lipoprotein levels does manifest itself

For reasons of convenience and availability of material the earliest studies made concerning the possible association of lipoproteins with coronary heart disease were made on patients with established clinical coronary heart disease. The objections to the use of such clinical material as a final group were reviewed in detail in Chapter II, where it was demonstrated however that such material is an excellent starting point in this problem. As was also pointed out earlier, the alternative to the use of such material is to study a very large number of apparently healthy people and then to watch the evolution of coronary heart disease *in this group. Such studies would allow not only for proof* of association of lipoproteins with sub-clinical coronary heart disease but also a determination of how early in the sub-clinical phase of the disease any abnormality of lipoproteins is present. Both types of studies have by now been completed with highly conclusive results and the results of both types of studies will be presented below

THE STUDY OF LIPOPROTEINS IN PATIENTS WITH CLINICALLY MANIFEST CORONARY HEART DISEASE

While the study of patients with clinically established coronary heart disease leaves undetermined the issue of whether the clinical event might have possibly caused any abnormality discovered in serum lipoproteins, the great availability of clinical material *without a long delay period* such as a prospective followup study entails made this the procedure of choice for start-

nent is that the control subjects be closely comparable to the clinically diseased subjects except for the one fact that the control subjects do not show clinically-manifest coronary heart disease. It is of no moment whatever to obtain a group of subjects as controls who are free of any possible tinge of sub-clinical coronary heart disease

Studies have been made of all the four major low-density lipoprotein classes, s_f0-12, s_f12-20, s_f20-100, and s_f100-400 in several age categories of males with and without clinical coronary heart disease in the form of documented myocardial infarction and in several age categories of females with and without clinical coronary heart disease The mean values for each of these lipoprotein classes in the subjects with clinical coronary heart disease and their matched controls are presented in Table I. It is evident from statistical analyses of these data for the sub-segments of the entire series of patients where there are adequate numbers of cases or for the entire series of cases and their age-and sex-matched controls, that the following is true:

(1) The s_f0-12 lipoproteins are significantly and appreciably higher in the clinical coronary heart disease cases than in their matched controls.

(2) The s_f12-20 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls

(3) The s_f20-100 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls

(4) The s_f100-400 lipoproteins are significantly and appreciably higher in the coronary disease cases than in their matched controls

The first large step forward can be taken, namely, to make the statement that the low-density serum lipoproteins are distinctly different, on the average, in patients with clinical coronary heart disease from those in their matched controls. It can be stated further that elevated levels of several serum lipoprotein classes are in some way associated with clinical coronary heart disease. Next must come the issue of whether *independent* information is provided by the measurement of *each* of these four lipoprotein classes.

trol subjects arises. Certain aspects of the choice of control subjects should be obvious, among these are such aspects as matching the cases of clinical coronary heart disease by sex, age, *and by general source of origin of the subjects. Since ideally* the study to be described subsequently is the one of choice, namely, where the coronary disease group arises de novo out of a previously studied large population sample, it is desirable in this study which compares persons with and without overt clinical coronary heart disease that as nearly as possible the control subjects be representative of the population segment out of which the clinical coronary disease cases had arisen. For example, it would be extremely poor matching if one were to use indigent patients with coronary heart disease as the disease subjects and a well-to-do population sample as the control subjects, or vice versa. This is not an academic matter at all, since the problem of selection of sources of clinical material is a very serious one often inadequately appreciated by clinical investigators.

One source of confusion has especially plagued the minds of many who have considered the evidence relating blood lipid findings with coronary heart disease. This is the question of whether or not the control subjects are free of coronary atherosclerosis First of all, it should be stated that this entire question *of the difference in blood lipids between subjects with clinical* coronary heart disease and control subjects is being developed wholly without any reference to atherosclerosis. Hence, there is simply no need whatever to ask the question of whether or not the control subjects are free of coronary atherosclerosis Second, even if we were to ask the question of whether there does exist sub-clinically some degree of coronary heart disease going on in those who have not yet manifested clinical symptoms, the fact that the answer is, yes, is wholly immaterial to the issues at hand. At this point, we are simply asking the question, "Is there a difference in lipoprotein levels of the various lipoprotein classes between those individuals who have demonstrated documented clinical coronary heart disease and those who have *not* demonstrated clinical coronary heart disease?" There is no inference, *intent to infer, or effort to prove that subjects chosen as controls* are free of sub-clinical coronary heart disease. All that is perti-

In essence the question to decide is whether S_f12-20 lipoproteins are *intrinsically* elevated in clinical coronary heart disease or whether they are elevated simply as a reflection of the elevation in S_f0-12 lipoproteins which characterizes clinical coronary heart disease. Perhaps another way to express this concept more clearly would be to ask the question, "If *all other things* were equal concerning the cases of clinical coronary heart disease and the matched controls, would the S_f0-12 lipoproteins still be elevated in the coronary disease cases?" Similar questions could be asked for the observed elevation in level of the S_f12-20 lipoproteins, the S_f20-100 lipoproteins, and the S_f100-400 lipoproteins, respectively. This approach can be made more simply if at first the total group of lipoproteins from S_f0 to S_f400 is subdivided into two major classes, S_f0-12 and S_f12-400 bands instead of into four groups. Then if the cases of documented myocardial infarction are matched with random control cases *at the same* S_f0-12 lipoprotein levels, is it true that the S_f12-400 lipoproteins are *still* elevated in the coronary disease cases relative to those in the matched controls? The direct tests of this issue are presented in Table II. The results there provide excellent evidence that the cases of myocardial infarction, matched with the control cases upon S_f0-12 lipoprotein level, do

TABLE II

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f12-400 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age, sex, and upon S_f0-12 lipoprotein levels)

Group	*Number of Cases*	*S_f0-12 Lipoprotein Level (mg/100ml)*	*S_f12-400 Lipoprotein Level (mg/100ml)*
40-49 year old male Myocardial Infarction Survivors	113	420.4	321.6
40-49 year old Matched Controls	113	422.2*	255.4
	Difference (Myocardial Infarctions − Controls)		+ 66.2 ($p << 0.001$)

*The slight differ...
controls indi...

TABLE I

SERUM LIPOPROTEIN LEVELS IN PERSONS WITH AND WITHOUT OVERT CLINICAL CORONARY HEART DISEASE

(Myocardial Infarction as Criterion)*

MALES	*Mean Age* (*years*)	*Number of Cases*	*Mean S_f0-12 Level (mg/100ml)*	*Mean S_f12-20 Level (mg/100ml)*	*Mean S_f20-100 Level (mg/100ml)*	*Mean S_f100-400 Level (mg/100ml)*
30-39 year age group						
Myocardial Infarction	31.8	11	485.0	104.3	152.1	72.3
Matched Controls	34.8	834	356.2	51.5	92.5	52.0
40-49 year age group						
Myocardial Infarction	44.5	113	420.4	88.7	134.3	98.7
Matched Controls	44.5	399	382.9	57.0	108.5	67.2
50-59 year age group						
Myocardial Infarction	54.0	210	413.4	83.3	124.3	77.3
Matched Controls	54.0	153	385.3	56.2	106.0	60.0
60-69 year age group						
Myocardial Infarction	63.9	144	407.7	82.2	121.2	61.7
Matched Controls	63.9	35	365.5	52.5	82.0	43.5
FEMALES						
35-69 year age group						
Myocardial Infarction	57.2	59	426.8	110.8	116.4	99.2
Matched Controls	57.2	110	367.0	54.5	87.8	26.0

*All myocardial infarction cases represent survivors, eight weeks or more beyond the acute episode.

In essence the question to decide is whether s_f12-20 lipoproteins are *intrinsically* elevated in clinical coronary heart disease or whether they are elevated simply as a reflection of the elevation in s_f0-12 lipoproteins which characterizes clinical coronary heart disease. Perhaps another way to express this concept more clearly would be to ask the question, "If all *other things* were equal concerning the cases of clinical coronary heart disease and the matched controls, would the s_f0-12 lipoproteins still be elevated in the coronary disease cases?" Similar questions could be asked for the observed elevation in level of the s_f12-20 lipoproteins, the s_f20-100 lipoproteins, and the s_f100-400 lipoproteins, respectively. This approach can be made more simply if at first the total group of lipoproteins from s_f0 to s_f400 is subdivided into two major classes, s_f0-12 and s_f12-400 bands instead of into four groups. Then if the cases of documented myocardial infarction are matched with random control cases *at the same* s_f0-12 lipoprotein levels, is it true that the s_f12-400 lipoproteins are *still* elevated in the coronary disease cases relative to those in the matched controls? The direct tests of this issue are presented in Table II. The results there provide excellent evidence that the cases of myocardial infarction, matched with the control cases upon s_f0-12 lipoprotein level, do

TABLE II

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f12-400 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age, sex, and upon S_f0-12 lipoprotein levels)

Group	Number of Cases	S_f0-12 Lipoprotein Level (mg/100ml)	S_f12-400 Lipoprotein Level (mg/100ml)
40-49 year old male Myocardial Infarction Survivors	113	420.4	321.6
40-49 year old Matched Controls	113	422.2*	255.4
	Difference (Myocardial Infarctions-Controls)		+ 66.2 (p<<0.001)

*The slight d[illegible]
controls in[illegible]

show a higher mean s_f12-400 lipoprotein level than do the controls. Therefore, evidence is at hand of the independent association between coronary heart disease and the s_f12-400 lipoprotein levels. Stated otherwise, while we get evidence from the measurement of s_f0-12 lipoprotein levels concerning coronary heart disease, we derive *additional* and truly independent information from the measurement of the s_f12-400 lipoprotein levels.

Similarly, the problem can be approached the other way around. If the documented cases of myocardial infarction are matched with random control cases at the same s_f12-400 lipoprotein level, is it true that the s_f0-12 lipoprotein levels are still elevated in the coronary disease cases as compared with the matched controls? A direct test of this point was made, the results of which are presented in Table III. Those results indicate clearly that even when the myocardial infarction cases are matched with the control cases at the same values of the s_f12-400 lipoproteins, the myocardial infarction cases still show a significantly and appreciably higher level of s_f0-12 lipoproteins than do the matched controls. Therefore, this provides direct evidence for the independent association of the s_f0-12 lipoproteins with coronary heart disease. Thus, while we get evidence from the measurement of the s_f12-400 lipoprotein levels concerning coronary heart disease,

TABLE III

DEMONSTRATION OF THE INDEPENDENT ELEVATION OF S_f0-12 LIPOPROTEIN LEVELS IN MYOCARDIAL INFARCTION CASES IN COMPARISON WITH MATCHED CONTROLS

(Myocardial infarction cases matched with random controls upon age, sex, and upon S_f12-400 lipoprotein levels)

Group	*Number of Cases*	*S_f12-400 Lipoprotein Level (mg/100ml)*	*S_f0-12 Lipoprotein Level (mg/100ml)*
40-49 year old male Myocardial Infarction Survivors	113	321 7	420 4
40-49 year old Matched Controls	113	322 8*	381 9
Difference (Myocardial Infarctions Controls)			+ 38.5 (p << 0 001)

*The slight difference in S_f12-400 lipoprotein level between the infarction cases and the controls indicates how well the two groups were matched upon this variable.

we derive additional and independent information from the measurement of the s_f0-12 lipoprotein levels

Looking ahead to some of the applications of these findings, it becomes apparent why such information is crucial. If two independent groups of lipoproteins determine a person's status with respect to coronary heart disease, it is clear that the measurement of only *one* of these groups cannot possibly provide a complete picture of that person's status. A person might, for example, be quite satisfactory in terms of his level of s_f0-12 lipoproteins and hence his outlook with respect to coronary disease be considered good on this basis, but on the other hand with an enormously elevated level of s_f12-400 lipoproteins the outlook would be changed to a poor one in spite of the favorable level of the s_f0-12 lipoproteins.

In an entirely analogous manner each of the subcomponents of the s_f12-400 group of lipoproteins, namely the s_f12-20, s_f20-100, and s_f100-400 lipoproteins can be tested for independent *association* with clinical coronary heart disease. This has been done successively for each of these lipoprotein classes[15]. It can be stated that s_f12-20 lipoproteins, s_f20-100 lipoproteins, and s_f100-400 lipoproteins, respectively, are all *independently* associated with clinical coronary heart disease

In summary, the study of established clinical coronary heart disease (utilizing documented myocardial infarction cases) is that low-density lipoproteins of the blood, at least of these four classes, the s_f0-12, 12-20, 20-100, and a 100-400 classes, are significantly elevated in clinical coronary heart disease and that each class of lipoproteins provides information independent of that provided by all the others. *Therefore the* [illegible]

[illegible] that there exist certain potential pitfalls in the application, for predictive purposes in the subclinical phase of coronary heart disease, of information derived from the study of after-the-fact cases of clinical coronary heart disease. Among such potential pitfalls is the possibility that a clinical episode of coronary heart disease itself is the cause of the lipoprotein elevation. The only way to evaluate this possibility

is to show whether the association between lipoprotein levels and coronary heart disease holds *during the sub-clinical phase,* well in advance of the clinical episode. This involves the study of lipoprotein levels in a reasonable sample of the population-at-large with follow-up observation for the development of de novo clinical coronary heart disease.

THE PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN SERUM LIPOPROTEINS AND CORONARY HEART DISEASE IN ITS SUB-CLINICAL STATE

The major potential value of what association exists between lipoproteins and coronary heart disease lies in the extent of such association during the sub-clinical phase. Any association demonstrated for the sub-clinical phase provides immediately information of potential value in the advance prediction of clinical coronary heart disease and of potential value in the guidance of a program for prevention of clinical coronary heart disease It was recognized early in the study of this problem that development of the information concerning the nature of the association of the sub-clinical coronary heart disease with serum lipoproteins was absolutely essential The establishment of the relationship of the serum lipoproteins with *clinical* coronary heart disease was an early step, possible because of the ready availability of material Those studies did provide a great deal of information of use while the results of the prospective study in the sub-clinical phase were awaited. The essence of a study designed to determine whether the association that has been proven between serum lipoproteins and clinical coronary heart disease also holds in the sub-clinical phase centers about follow-up observations A large population sample of individuals in overt health, that is, free of any evidence of clinical coronary heart disease, is studied with respect to lipoprotein levels Then, for a period of one or more years such *individuals are observed without any effort being* made to alter their lipoprotein levels and, indeed, without them being aware of the findings of the lipoprotein analysis. If the sample of the population studied is sufficiently large, then over a period of one to three years there is expected a reason-

able incidence of development of manifestations of clinical coronary heart disease in the form for example of angina pectoris, myocardial infarction, or death due to coronary heart disease. Since angina pectoris is a subjective diagnosis, this is the least safe to use as a clinical manifestation of the development of coronary heart disease. Hence in the considerations of an association between the sub-clinical phase of coronary disease and lipoproteins, the development of angina pectoris was not used as a primary criterion However, documented myocardial infarction, coronary thrombosis with death, and sudden death due to coronary heart disease were used as acceptable events of a clinical type to identify those individuals who passed from the sub-clinical phase of coronary heart disease to the clinical phase. If the lipoprotein association with coronary heart disease which was proven above with respect to the clinical phase also holds in the sub-clinical phase, it would be expected that the mean level of the various classes of lipoproteins in those individuals in the population sample who develop clinical coronary heart disease will be the same as the mean level found in the cases of established clinical coronary heart disease This would be so unless the clinical coronary heart disease has of itself altered the lipoprotein levels or that some factor attendant upon clinical coronary heart disease such as alteration in diet or medication has altered the lipoprotein levels If the lipoprotein elevation is an abnormality present before the *clinical event* and is unaltered by the clinical event itself, then it would be expected that the lipoprotein level determined in a group of people before they have a myocardial infarction should be the same as in such groups of people studied after the infarction

The requisite large scale follow-up study has now been completed[16, 17] Several sources of men in clinical health were utilized to provide lipoprotein samples before the follow-up observation period These sources included:

(1) Persons involved in the Framingham United States Public Health Service Heart Project.

(2) Employees of the Eastman Kodak Corporation.

(3) Employees of United Air Lines

(4) Employees of the Los Angeles Civil Service Commission.

(5) Employees of Pan American Airlines.

(6) Employees of the University of California Radiation Laboratory.

In all there were 4,088 subjects under study. During a one to three year follow-up period, the period being variable for the various sources, there occurred 26 cases of documented myocardial infarction, coronary thrombosis, or coronary heart disease with death in individuals who had been previously classified at the time of entry into the study as being in clinical health. Since being in clinical health means only that overt manifestations of coronary heart disease are absent, this is of course tantamount to saying that such individuals were *in various stages of the development of sub-clinical coronary heart disease,* since this is the real meaning of sub-clinical coronary heart disease. In Table IV are listed the cases of proven documented clinical coronary heart disease which have evolved out of the population sample under follow-up together with their lipoprotein values for the various classes. Also in Table IV are given the mean values for the matched population sample itself out of which the cases have arisen, matched by age with the cases of documented de novo coronary heart disease (according to the above-listed criteria). These data show clearly that the persons who later develop clinical coronary heart disease are those who were previously shown to have elevated lipoproteins of the four low-density lipoprotein classes, S_f0-12, S_f12-20, S_f20-100, and S_f100-400. Furthermore, the extent of lipoprotein elevation that had characterized the de novo cases one to three years before is closely similar to that found previously *for established cases of coronary heart disease* described above These data establish conclusively that the lipoprotein associations previously proven for clinical coronary heart disease *also hold for the sub-clinical phase, at least* one to three years before the clinical phase. This of course implies that lipoprotein measurement *must* have predictive value in selecting out the likely candidates for the future development of clinical coronary heart disease. The exact manner in which such data are used for such predictive purposes will be treated in Chapter V.

However, at the present time it is important to point out that the data derived from the prospective follow-up study show clearly that none of the concepts concerning lipoproteins and coronary heart disease derived from the study of the established clinical entity were in any way incorrect or misleading. Indeed the agreement between the study of established coronary heart disease and de novo coronary heart disease could hardly have been better.

There had previously existed much indirect evidence which would have suggested that the abnormality in blood lipids,

TABLE IV (a)

LIPOPROTEIN LEVELS IN 25 MEN (DETERMINED WHILE THEY WERE CLINICALLY HEALTHY) WHO SUBSEQUENTLY DEVELOPED DOCUMENTED CLINICAL CORONARY HEART DISEASE

(1 to 3 year follow up period)

Case	*Age at Study*	S_f*0-12* *(mg/100ml)*	S_f*12-20* *(mg/100ml)*	S_f*20-100* *(mg/100ml)*	S_f*100-400* *(mg/100ml)*
1	34	576	85	155	139
2	35	719	139	271	131
3	37	309	58	228	130
4	40	418	72	110	121
5	40	452	63	251	181
6	40	388	52	74	16
7	40	473	90	179	237
8	42	206	81	217	118
9	42	345	76	110	56
10	44	461	92	99	47
11	45	403	112	101	137
12	46	520	128	175	43
13	47	410	65	131	119
14	49	329	72	92	52
15	49	414	81	164	38
16	49	318	58	123	67
17	49	403	81	166	85
18	51	580	65	139	16
19	51	497	110	125	110
20	51	605	116	179	72
21	51	403	67	128	36
22	52	482	56	103	52
23	56	318	119	96	43
24	57	381	78	108	67
25	57	521	130	136	26
26	58	535	134	190	94

expressed in the form of an elevation of certain serum lipoproteins, *would* characterize individuals *in advance* of the development of clinical coronary heart disease. Such evidence derived from the abnormalities in lipids in diabetes mellitus (pre-insulin period at least), in nephrosis, and in myxedema, and in a variety of familial entities—all of which are characterized by premature coronary heart disease. In all of these cases the lipid abnormality it known to precede the development of vascular disease. However these were all special situations, and while they provided highly suggestive leads, it was essential, in dealing with the problem of coronary heart disease in the vast bulk of the population, to prove directly, as it has now been done conclusively, that the blood lipid abnormality does indeed precede the clinical development of coronary heart disease. The ability to make predictions concerning the rate of development and severity of sub-clinical coronary heart disease one to three years in advance of its conversion to clinically-manifest disease is of course a major step forward. Next it is important to ask the question, "Is such predictability limited to one to three years before the development of overt, clinical coronary heart disease?" The evidence just presented does not *limit* the predictability of future coronary disease from lipoprotein measurement to three years

TABLE IV (b)

COMPARISON OF MEAN LIPOPROTEIN LEVELS FOR 26 DE NOVO CLINICAL CORONARY DISEASE CASES WITH THOSE FOR THE AGE MATCHED POPULATION SAMPLE FROM WHICH THEY AROSE (MFN)

	Mean Age (years)	*Mean S_f 0-12 (mg/100ml)*	*Mean S_f 12-20 (mg/100ml)*	*Mean S_f 20-100 mg/100ml)*	*Mean S_f 100-400 mg/100ml)*
De Novo Documented Clinical Coronary Disease Group	46.6	442.2	87.7	118.3	87.3
Age-Matched Healthy Population Sample out of which the coronary disease cases arose	46.6	386.0	57.6	110.3	68.0
Difference (De Novo Coronary Cases—Healthy Population Sample)		+ 56.2	+ 30.1	+ 38.0	+ 19.3
		$p << 0.01$	$p << 0.001$	$p < 0.01$	$p \sim 0.05$

Rather, what is meant is that such evidence by and of itself only allows assurance of the predictability for one to three years, since this was the time period of the follow-up study. However it is possible through incorporation of other findings referable to lipoprotein levels in individuals to demonstrate that the abnormality in serum lipoproteins is undoubtedly present a much longer period than three years before the development of clinical coronary heart disease. All the evidence available suggests that the lipoprotein abnormality may be used to pre-select individuals who are likely to develop clinical coronary heart disease as many as ten or twenty years before the development of the overt clinical entity.

In order to determine directly the maximum period before the development of clinical coronary heart disease that the lipoproteins may be used in prediction of risk of future clinical coronary heart disease, it would be necessary that the follow-up studies described above be carried on for five, ten, fifteen, twenty or twenty-five years. These follow-up studies will of course be carried on as an extension of those that have already been done. However, it is not necessary to await the results of the five, ten, fifteen, or twenty year follow-up periods to determine the answer of duration of predictive value, since *it is* possible to attain this answer now. The basic question underlying the problem of how long *beyond* three years the predictive value of lipoprotein measurement is valid is that of knowing whether people in the population tend to retain their relative positions *with respect to each other* in terms of lipoprotein values. This point may be illustrated by considering two representative individuals in the population. The data presented above would indicate that, if we study one individual with high lipoprotein levels and another individual with low lipoprotein levels, during the one to three year period following the lipoprotein measurement the person with high values is more likely to develop coronary heart disease than the one with low values. This is true because data accumulated already have shown that the average value and the distribution of values of the lipoproteins studied in advance are higher in those who go on to develop coronary disease than in those who do not. Therefore if studies had demonstrated that

the person with high lipoprotein levels had remained high for five years, and the person with low levels had remained low for five years before this study was started, then the prediction would be valid for an additional five year period. This is evident, since it would have been possible to determine five years earlier that the same relative position characterized the two people under consideration. Similarly if instead of 5 years such consistency in *relative* position with respect to lipoprotein level had been maintained for ten or fifteen years before the study, then the predictive value would have held for this corresponding ten or fifteen year period. The only situation in which the prediction available from the lipoprotein levels would have not been valid would arise when two individuals alter their relative positions appreciably on the lipoprotein scale over the five, ten, or fifteen year period under consideration. Again, to settle this issue directly would require that the population of individuals be followed with serial blood sampling for a period of five, ten, or fifteen years of adult life. Since the technical development of lipoprotein measurement is now only ten years old, it has not been possible to follow large numbers of individuals this long. However, it has been possible to follow individuals at every age period in adult life for a shorter period of time. That is, it has been possible to study individuals at 20 years of age during a two to five year period to the age of 22 or 25 years, individuals at 25 years of age to the age of 27 or 30 years, individuals 30 years of age to the age of 32 or 35 years, individuals at 35 years of age to the age of 37 to 40 years, and so on up to the age of sixty years. It has been shown that for these various spans, 20 to 25, 25 to 30, 30 to 35, and so on up to 55 to 60, individuals tend very strongly to retain their relative ranking on the lipoprotein scale. Since this has been shown to be true for every five year period between 20 and 60 years, there appears to exist *no* period during adult life when individuals tend to shift around in relative positions on the lipoprotein scale. Therefore it can be stated that individuals tend to retain their relative lipoprotein ranking in the population very well. This means that the abnormality in lipoproteins which was directly proved to be predictive of coronary heart disease at least one to three years before the development

of clinical coronary heart disease can be estimated to exist, in general, at least for periods of the order of ten or twenty years of adult life. Candidates for future clinical coronary heart disease can therefore be identified some ten to twenty years before the disease becomes overt, which means that the opportunity for institution of preventive measures is excellent.

There is no inference in any of these statements that the lipoprotein levels in a particular individual remain absolutely constant throughout adult life There does exist some short-term fluctuation and some long term fluctuation in individuals. However, in general, such fluctuations in levels of the crucial low-density lipoproteins are small enough such that persons in the lowest 10 or 20% of the population distribution tend to remain there, in spite of fluctuation, whereas persons in the highest 10% of the population tend to remain there. This, rather than the minor fluctuations that do occur, is the important issue at hand. One qualification of these statements is necessary. It will be shown later (Chapter IX and X) that diet and body weight are related to lipoprotein levels Therefore if an individual should significantly alter his dietary pattern and his body weight, it would be expected that his relative ranking in lipoprotein levels would be altered But such dietary and weight alterations are readily determined and hence need never provide confusion concerning the person's status Similarly certain clinical entities such as nephrosis or myxedema are associated with gross alterations in lipoprotein levels Hence no surprise would be occasioned by the occurrence of a shift in relative ranking of an individual with respect to others if he should develop clinical nephrosis or myxedema

The demonstration that lipoprotein levels are elevated during the sub-clinical phase of coronary heart disease years in advance of overt clinical manifestation is beyond reasonable doubt This finding carries with it the direct implication and the information which make it possible to predict the risk of future overt clinical coronary heart disease in individuals through blood lipoprotein measurement. The manner of use of the lipoprotein data for this predictive purpose and the extent of prediction possible will be elaborated in detail in Chapter V.

Chapter IV

THE BLOOD PRESSURE FACTOR IN CORONARY HEART DISEASE

It is a source of amazement that at this late date there should exist so much confusion with respect to the issue of the nature of the relationship of habitual blood pressure levels with coronary heart disease, both sub-clinical and clinical A review of the evidence in the literature concerning the blood pressure and coronary heart disease indicates clearly that the actual data pertaining to this subject are not at all confusing, but rather that the interpretation of such data has often been faulty and has led to the current divergence and haziness of "authoritative" views. The specific problems of concern here are twofold.

(a) The extent of difference, if any, in the habitual blood pressure in those persons developing sub-clinical coronary heart disease at an excessive rate in comparison with those developing the disease at a slow rate

(b) If the habitual blood pressure is significantly related to the rate of development of sub-clinical coronary heart disease, it must be determined whether information is thereby provided independent of the information provided by the blood lipoprotein measurements

It is obvious why these are crucial issues in coronary heart disease For, if the blood pressure is significantly related to the development of sub-clinical coronary heart disease, and if the information is *independent* of the lipoprotein information, then an additional tool, or an additional factor, is available for evaluation of any person with respect to the risk of later clinical coronary heart disease.

The evidence concerning the blood pressure is derived from many sources and types of evidence Some of these sources are

indirect but have provided valuable clues crucial for a critical evaluation of the role of habitual blood pressure levels in coronary heart disease. The problem at hand, with respect to coronary heart disease, can be stated in a frame of reference similar to that for the blood lipoproteins. If one were to rank a large group of individuals in overt health upon their habitual blood pressures, without any knowledge of other factors, would it be true that coronary heart disease occurs with a greater frequency in those with elevated blood pressures than in those without such elevation? However, before consideration of the relevant data, let us review much of the ancillary evidence which can be regarded as being in the form of clues and suggestions. First, there is a long-standing clinical impression that coronary heart disease and hypertensive cardiovascular disease are in some way related. So strong has been this impression that in the minds of some physicians the two phenomena, hypertension and coronary heart disease, have been regarded as facets of the same problem. The direct, critical evidence relating these two phenomena is not nearly so good as the clinical impression would indicate. Second, there exists a wide spectrum of experimental data which suggests that hypertension is related to the development of arteriosclerosis of the large and medium-sized arteries. While evidence concerning arteriosclerosis is to be considered as suggestive, it will not be made the basis of any definitive case for the findings with respect to hypertension. The clinical and pathological literature show frequent recording of observations that areas of the arterial tree subjected to excessive pressure are characterized by premature and excessive degrees of arteriosclerosis. One such item of evidence arises from the study of the region of the aorta before and after a coarctation. Many pathology texts comment on the high degree of sclerosis in the area before the coarctation (the high pressure side) versus the much lower degree of sclerosis in the area after the coarctation (the low pressure side)[18]. There also exists experimental evidence derived both from studies of the dog and of the rabbit which indicates that the blood pressure is an important factor in promoting the degree of arteriosclerosis in the arterial tree. Wakerlin[19], in some critical studies in dogs, performed the following experiment. On one

group of dogs he performed a Goldblatt operation with constriction of the renal artery to produce a hypertension in the dog, whereas on the second group he performed a sham operation without constriction of the renal artery. Both groups of dogs were then maintained on an atherogenic regimen including thiouracil (for suppression of thyroid function) and the cholesterol feeding. Steiner and Kendall[20] had previously shown that in dogs this combined regimen would produce elevation of the blood lipids and subsequent arteriosclerosis. Wakerlin found that the degree of arteriosclerosis in the major arterial vessels was much greater in the group of hypertensive dogs than in the group of sham-operated non-hypertensive dogs, even though the average extent of elevation of the blood lipids and lipoproteins was the same for the two groups of animals This represents a rather clear-cut demonstration that the elevated blood pressure was itself a major factor in promoting arteriosclerosis Similar results were obtained by Heptinstall and Porter[21] in the study of the experimental rabbit being fed cholesterol. In this case hypertension was produced by a clip on the renal artery. Again, it was shown by these workers that the degree of arteriosclerosis in the aorta was much more marked in the hypertensive rabbits than in the normotensive group, both groups having experienced comparable blood lipid elevations

Turning now to the direct clinical evidence with respect to the relationship of hypertension with the entity of coronary heart disease *rather than with arteriosclerosis*, one finds a vast mass of literature replete with apparently conflicting statements and opinions One statement commonly found in textbooks and in the literature is that hypertension in the female sex is a factor in coronary heart disease whereas it is not a factor in the male sex. Another variant of this same statement is that coronary heart disease is rarely seen in a young woman unless she is a diabetic or a hypertensive. It is important to examine critically the evidence which has been claimed to show the elevated blood pressure is a factor in the female sex but is not a factor in the male sex, since with careful scrutiny of the data, this concept is *not* supported.

THE CHOICE OF CLINICAL MATERIAL FOR THE STUDY OF THE HYPERTENSION FACTOR

The basic question at hand is, "Do persons with habitual elevation in blood pressure level develop *sub-clinical* coronary heart disease at a greater rate than persons without such elevation?" It is a corollary of this question to ask, "Do persons with habitual elevation in blood pressure show a higher attack rate of clinical coronary heart disease than do persons *without* such elevation? If the answer to such questions is in the affirmative, then it would be anticipated that the *average* blood pressure (measured *in advance* of the appearance of clinical coronary heart disease) will be higher for those who do develop clinical coronary heart disease in a specified time interval than for those who do not. Further it would be anticipated that there will be a shift in the distribution of blood pressures toward higher values in the group which later develops clinical coronary heart disease than in the group which does not do so in the same specified time interval. Ideally the appropriate source of clinical material for such a study is a large group of apparently healthy individuals for whom blood pressure measurements are available. Out of an adequately large group of persons there will develop a sub-group with overt clinical manifestations of coronary heart disease in a one-year, two-year, or longer period. The outgrowth of an adequately large group of subjects in the clinically-overt coronary disease group during any specified follow-up period is simply a matter of starting with a sufficiently large population sample in [illegible] Fortunately [illegible] ded definitive [illegible] respect to the issue of antecedent blood pressure elevation and coronary heart disease development. Yater[22] has provided the data from one such study and Dawber and co-workers[21] have provided the data from another, the large-scale Framingham Heart Project of the National Heart Institute. The evidence from both these studies is unequivocal and hence can provide the requisite information without recourse to any of the studies of less definitive character. However, since some of less definitive studies in the clinical literature have influenced medical thinking on this subject and have led to certain highly erroneous statements

and conclusions, it is important to review them here, lest the physician be left with the impression that there may be controversial aspects of the problem. It is important to state at the outset that *no contradictory evidence* arises from *any* of the sources of evidence The apparently contradictory conclusions represent erroneous interpretations of the clinical findings themselves.

As recently as 1954, Wright, Marple and Beck in their book *Myocardial Infarction*[24] *cite the work of Master, Garfield and* Walters[25] as follows, "These authors concluded, therefore, that there was no close relationship between hypertension and coronary artery disease or coronary occlusion in males less than 65 years of age Hypertension did appear, however, to have an important relationship with coronary occlusion in women" That Wright and co-workers quoted this conclusion without further comment suggests that they were not *prepared to comment on its validity.* Indeed nowhere in their discussion of the relationship of hypertension to coronary heart disease did Wright and co-authors make any definite statement of their own concerning the relationship of these entities. Levine and Brown[26] had long before stated that, "A pre-existing hypertension is probably the most common etiologic factor in the development of myocardial infarction in the majority of cases" The physician reading such reference sources might readily conclude that some question exists as to whether antecedent hypertension exists in persons who develop clinical coronary heart disease, at least for men, or at least for men under *65 years of age. Yet, the evidence from clinical sources should* not lead to an equivocal position on this most important issue Why, then, does some question appear to exist?

The largest part of the confusion in the literature on this issue arises from two sources.

(1) The arbitrary definition of what constitutes hypertension.

(2) Having established an arbitrary definition of hypertension, the clinician's expectation that some large proportion, preferably over 50%, of cases of myocardial infarction should have had at least this degree of antecedent hypertension.

Neither an arbitrary definition of hypertension nor an

expectation that an arbitrary proportion of myocardial infarction cases would have shown antecedent hypertension by such arbitrary definition is helpful in this problem. The crucial issue was outlined previously, namely, whether or not the myocardial infarction cases showed a distribution of antecedent blood pressures shifted to a higher level and a higher average blood pressure than persons free of clinical coronary heart disease in the same follow-up period For, if such a difference in average blood pressure and distribution of blood pressure values does exist, then it follows unequivocally that blood pressure elevation is associated with sub clinical coronary heart disease and that the blood pressure level can be utilized as a predictive measure with respect to the development of future clinical coronary heart disease To be sure, the greater the difference in the average antecedent blood pressure values between the persons who do develop clinical coronary heart disease and those who do not during the same specified time interval, the more the blood pressure measurement will be helpful in prediction of the risk of future clinical coronary heart disease for currently healthy persons. But no statistical or medical consideration justifies the requirement that any arbitrary proportion of the de novo myocardial infarction cases exceed any arbitrary blood pressure level When analyzed correctly, every reported study known to the present author clearly supports the view that antecedent blood pressure elevation is distinctly associated with the development of sub-clinical coronary heart disease and that the blood pressure is an important predictive measure in determination of the risk of future clinical coronary heart disease for *both men and women at all ages* While some of the reported studies utilized clinical material of somewhat doubtful value, the evidence from them as a whole is so overwhelming as to leave no doubt about the findings and their proper interpretation The chief criticism of the usual clinical material is that the cases of myocardial infarction are either from hospital admissions or from the office practise of the reporting physician In these studies some authors utilized antecedent blood pressure measurements for such cases either from their own office records or from hospital charts The doubt we must entertain centers around the very fact that a measurement

and conclusions, it is important to review them here, lest the physician be left with the impression that there may be controversial aspects of the problem. It is important to state at the outset that *no contradictory evidence* arises from *any* of the sources of evidence. The apparently contradictory conclusions represent erroneous interpretations of the clinical findings themselves.

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ersons, taken as representative of the population-at-large, by the ame criteria of blood pressure limits (160 mm Hg systolic or 100 mm Hg diastolic or both), such a group of persons at age 58.5 years would be expected to show 28 to 30% with a classification of hypertension. Since Levine and Brown found 40% of their patients to qualify (plus additional cases with *clinical* evidence of pre-existing hypertension) it is clear that in this series, the mean blood pressure was high and the distribution of values shifted

tion. In this group were 194 men (average age 58.9 years) and 80 women (average age 59.7 years). Of the entire group 173 patients, or 63%, were known to have had blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both, antecedent to their coronary occlusion. Since the antecedent blood pressure was not known for many patients, the true incidence of pressures above these limits must have been greater than the 63% recorded by Rathe. From the Master data it would be anticipated that approximately 57% of individuals of this average age would show blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both. Since the Rathe incidence of 63% is a *minimum* value, it appears that his series of patients with clinical coronary heart disease had had antecedent elevation of blood pressures in comparison with those in the population-at-large.

Chambers[27] reported on a series of 100 cases of myocardial infarction (72 males and 28 females). For 85 of these 100 cases the blood pressure during *the pre-infarction* period was known. As criteria for hypertension he required a systolic pressure of 150 mm Hg or more plus a diastolic pressure of 90 mm Hg or more. Seventy-four of the 100 cases were known to have been hypertensive by these criteria, while for 15 cases the antecedent blood pressure was unknown. Therefore, *at a minimum*, 74% of his cases were hypertensive before the myocardial infarction. From the Master data, utilizing the criterion of diastolic pressure 90 mm Hg or higher, no more than 35% of the population-at-large would be hypertensive (and this is a *less* rigid criterion than that of Chambers). Therefore the 100 case series of Chambers showed a strik-

of the blood pressure for such persons *exists*, especially when we wish to compare such blood pressures with those in the population-at-large. For, if a person has a hospital chart record or an office record of previous blood pressure readings, there must have existed some medical complaint that had led him either to a physician's office or to a hospital, unless he were accustomed to routine periodic medical check-ups. Thus the possibility that such blood pressures are not representative of those in the population-at-large definitely exists, and indeed they may be seriously biassed in the direction of elevated pressures. On the other hand, in some of the reported series of cases antecedent blood pressure records were unavailable for some of the cases of myocardial infarction. In such cases the authors utilized blood pressure readings taken on the patients during their hospitalization for the myocardial infarction itself. This type of blood pressure reading will, for many cases, be lower than the habitual blood pressure the particular person would have shown in the months or years before myocardial infarction, since it is well-known that the blood pressure may fall appreciably (and remain low for a long period) after myocardial infarction. Numerous of the workers were cognizant that in-hospital blood pressures might be biassed, and biassed in the direction of being too low as a measure of the particular patient's habitual blood pressure. Thus, some possible sources of bias exist that might yield too high a blood pressure for the cases of clinical coronary heart disease, whereas others exist that might yield too low a blood pressure. To what extent such biasses cancel each other out in some of the studies reported in the literature is problematical. However, with the necessary reservations in mind, it is worthwhile to consider the major literature reports on the relationship of blood pressure levels with myocardial infarction both in men and women at various ages.

Levine and Brown studied 145 patients with myocardial infarction. Of this group of patients 58 were known to have had pre-existing hypertension, using as a definition of hypertension a systolic pressure of 160 mm Hg. or more or a diastolic pressure of 100 mm Hg or more. The average age for this group of patients was 58.5 years. From the data of Master, Garfield, and Walters, based upon the analysis of data for 74,000 employed

persons, taken as representative of the population-at-large, by the same criteria of blood pressure limits (160 mm Hg systolic or 100 mm Hg diastolic or both), such a group of persons at age 58.5 years would be expected to show 28 to 30% with a classification of hypertension. Since Levine and Brown found 40% of their patients to qualify (plus additional cases with *clinical* evidence of pre-existing hypertension) it is clear that in this series, the mean blood pressure was high and the distribution of values shifted toward high levels in the persons experiencing myocardial infarction as compared with the population-at-large.

Rathe[27] analyzed the history in 274 cases of myocardial infarction. In this group were 194 men (average age 58.9 years) and 80 women (average age 59.7 years). Of the entire group 173 patients, or 63%, were known to have had blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both, antecedent to their coronary occlusion Since the antecedent blood pressure was not known for many patients, the true incidence of pressures above these limits must have been greater than the 63% recorded by Rathe. From the Master data it would be anticipated that approximately 57% of individuals of this average age would show blood pressures of over 140 mm Hg systolic, or 90 mm Hg diastolic, or both. Since the Rathe incidence of 63% is a *minimum value*, it appears that his series of patients with clinical coronary heart disease had had antecedent elevation of blood pressures in comparison with those in the population-at-large.

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ing elevation in blood pressure and a shift to higher values as compared with the population-at-large.

Doscher and *Poindexter*[28] *reported a series of 414 cases of* myocardial infarction observed between 1935 and 1948, including 334 men and 80 women. As a criterion for hypertension they required a *history of, or an observation post-infarction, of a dias-*tolic pressure of 100 mm Hg or more. Since no history was available for some of the cases and because infarction itself can have lowered observed *post-infarction pressures, the incidence of hyper-*tension reported by Doscher and Poindexter would have to be regarded as a minimum value. Since sufficient numbers of cases are available for several age *categories for both sexes, comparisons* are made in Table V between the hypertension incidence in the Doscher - Poindexter series and the population - at - large data of Master. For each age category and for both sexes the Doscher-Poindexter series shows a striking shift of blood pressures to high values in those persons developing myocardial infarction in comparison with the persons in the population-at-large.

Mintz and Katz[29] reported a series of 572 cases of myocardial infarction from the 1940-1945 experience at Michael Reese Hospital. For 308 of these cases the blood pressure values in the pre-infarction period were known Of this latter group 188 cases (61%) were known to have had diastolic blood pressures above 90 mm Hg The average age of the males in their series was 59 2 years; the average age of the females was 62.2 years. From the distribution of males and females in their series and the incidence of hypertension for the two sexes, it is readily calculated that approximately 50% of the men and 86% of the women had antecedent hypertension by their criterion. These values should be compared as follows with the analogous data of Master for the population-at-large, the 50% of men with coronary disease with a value of 35% for men in the population-at-large, the 86% of women with coronary disease with a value of 39% for women in the population-at-large Clearly, for both sexes, the Mintz and Katz series of cases of myocardial infarction shows a marked shift to high values of the blood pressure for persons later experiencing myocardial infarction.

Master, Garfield and Walters[25] presented data for 554 cases of

TABLE V

INCIDENCE OF HYPERTENSION BY AGE AND SEX IN DOSCHER POINDEXTER SERIES OF MYOCARDIAL INFARCTION CASES

(Criterion of Hypertension. Diastolic Pressure 100 mm Hg or Higher)

Males	*30-39 Years*	*40-49 Years*	*50-59 Years*	*60-69 Years*	*70+ Years*
Number of cases	(18 cases)	(85 cases)	(126 cases)	(83 cases)	(20 cases)
Incidence of Hypertension in Myocardial Infarction Cases	11%	29%	33%	42%	35%
Incidence of Hypertension in Population at large (Matched by age)*	3%	6%	11%	15%	Data not available
Females					
Number of cases	(1 case)	(5 cases)	(35 cases)	(27 cases)	(14 cases)
Incidence of Hypertension in Myocardial Infarction Cases	Too few cases	Too few cases	51%	41%	61%
Incidence of Hypertension in Population at-large (Matched by age)*			12%	16%	Data not available

*Population at large data are those of Master, Garfield, and Walters[28]

coronary occlusion in whom the status of antecedent blood pressures was evaluated. By Master's method hypertension is defined, for any age and sex group, as that blood pressure value exceeded only by 2.5% of the persons in the population-at-large. Therefore in comparing his infarction series with the population-at-large, the incidence of hypertension in the latter group by his criteria is always 2.5%. The comparison of Master's infarction series with the population-at-large is presented in Table VI. In both sexes, and for every age category where adequate data are available, there is a strikingly greater incidence of hypertension in the myo-

TABLE VI

INCIDENCE OF ANTECEDENT HYPERTENSION IN MYOCARDIAL INFARCTION CASES
(Based upon 554 Cases of Master and Co-workers[11])

Males *Age Group*	*Number of Cases of Myocardial Infarction*	*Incidence of Hypertension in Myocardial Infarction Cases (%)*	*Incidence of Hypertension in Population-at-Large* (%)*
35-39 years	18	16.7%	2.5%
40-44 years	66	25.8%	2.5%
45-49 years	80	27.5%	2.5%
50-54 years	121	28.9%	2.5%
55-59 years	105	25.6%	2.5%
60-64 years	61	31.2%	2.5%
Females			
35-39 years	4	75.0%	2.5%
40-44 years	9	44.4%	2.5%
45-49 years	9	77.6%	2.5%
50-54 years	18	77.8%	2.5%
55-59 years	28	64.4%	2.5%
60-64 years	32	78.2%	2.5%

*All values for the incidence of hypertension in the population-at-large are necessarily 2.5% in this tabulation by virtue of Master's definition of hypertension

cardial infarction cases than in the corresponding group from the population-at-large. Master, however, focussing on another aspect of the data, drew the opposite conclusion. He pointed out that hypertension (by his definition) was present *only* in 27% of the males. Since this meant that over 70% of men with coronary occlusion had had normal blood pressures, he stated, "The evident conclusion to be drawn is, that there is no very close relationship between hypertension and coronary artery disease and occlusion in the males, at least in those under sixty-five years of age." The really correct evident conclusion is that elevation in blood pressure is *strongly* related to development of coronary occlusion in men at every age investigated When 27% of the persons who *develop coronary occlusion are characterized* by blood pressures above a specified level in contrast with 2.5% of the persons who do not develop coronary occlusion in the same time period, we have at hand a fabulously strong association between coronary occlusion and antecedent elevation in blood pressure. The error in Master's reasoning lies in choosing an arbitrary blood pressure value (that above which lie only 2.5% of the population) and then

being disturbed by the fact that only 27% of the coronary occlusion cases had antecedent pressures above this level The real comparison is between 27% and 2.5%, rather than between 27% and 100%.

While it is clear from these several clinical series of myocardial infarction cases that antecedent blood pressure elevation characterizes persons developing clinical coronary heart disease, there remain the possible sources of bias described previously. We may therefore consider the evidence from two studies where such sources of bias do not exist One such study, the Framingham study of the National Heart Institute, has recently been reported by Dawber, Moore, and Mann[23]. This is a continuing epidemiological study of the extent of development of new cardiovascular disease in a cross-section of the population of the town of Framingham, Massachusetts. All the subjects in this cross-section of the population are examined by clinical and laboratory methods every two years and a careful followup is in progress continually to ascertain the development of such new events as myocardial infarction or other forms of coronary heart disease. The experience with four years of follow-up in this study yielded definitive results with respect to the relationship of blood pressure with the subsequent evolution of clinical coronary heart disease. There were 898 men between the ages of 45 and 62 years who represented the population at risk during the reported four year follow-up period At the time of the initial examination *none* of these 898 men showed evidence, clinical or laboratory, of definite coronary heart disease. During the four year period 48 of the men developed what were regarded as definite manifestations of clinical coronary heart disease, including one or more of the following entities. myocardial infarction, coronary occlusion, angina pectoris, myocardial fibrosis, or electrocardiographic evidence of myocardial infarction The original group of 898 men can be subdivided on the basis of blood pressure into two major groups, the normotensives on initial examination and those with varying degrees of hypertension, borderline or definite. For purposes of definition of normotension, Dawber and co-workers used the criterion that left arm blood pressures had to be below 140/90 mm Hg on independent observations by two physicians All other

subjects fit into one or another category, such as borderline hypertension, definite hypertension, and possible or definite hypertensive heart disease. The normotensive group, constituting 310 men, developed 8 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow-up period.* The remaining group (various degrees of hypertension by their criteria), constituting 541 men, developed 40 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow-up period. Thus for the "normotensive" group, the incidence rate of de novo clinical coronary heart disease was 26 cases *per 1000 persons at risk over the four year* period, whereas for the "hypertensive" group the incidence rate of de novo clinical coronary heart disease was 74 cases per 1000 *persons at risk over the same time period. This difference in attack* rates of de novo clinical coronary heart disease is significant and clearly supports the concept that elevation in blood pressure increases the risk of future clinical coronary heart disease. Stated otherwise, this evidence links elevation in blood pressure with the *sub-clinical* phase of coronary heart disease and indicates that the blood pressure is one predictive measure for ascertaining the risk a person carries for passing from the sub-clinical to the clinical phase of coronary heart disease.

Another wholly separate study provides evidence completely consistent with that derived from the Framingham study This is the analysis of Yater and co-workers[22] of 542 men who survived a documented myocardial infarction or who died of coronary heart disease while in the Armed Services. The average age of this group was approximately 33 years. For these men who developed their clinical coronary heart disease while in the Armed Service there was available to Yater the blood pressure values at induction examination, at which time all the men were free of recognizable clinical coronary heart disease. In order to have a control group whose blood pressures had been measured under as nearly identical conditions as for the coronary heart disease group, Yater utilized the induction blood pressures for 213 men who were service-connected amputees or who were otherwise wounded, none of

*Forty seven *of the 898 men were normotensive, but* had a history of cerebro vascular accident of rheumatic heart disease These are excluded from analysis

whom had overt coronary heart disease. The systolic pressures were found to be above normal (utilizing a criterion of 139 mm Hg systolic as the upper limit of normal) in 27.9% of the men (18 to 39 years of age) who subsequently developed clinical coronary heart disease contrasted with 8.9% of the men in the Army control group. Thus there was a three-fold increase in the incidence of high systolic pressures at Army induction for those who subsequently developed clinical coronary heart disease in comparison with those who did not. The same type of trend was evident for the diastolic blood pressures. Whereas 19.1% of the men who subsequently developed clinical coronary heart disease had shown diastolic blood pressures above 90 mm Hg at induction, only 3.8% of the Army control group had shown diastolic pressures above 90 mm Hg at induction. There was, therefore, a five-fold increase in incidence in prior diastolic blood pressure elevation above 90 mm Hg in the coronary disease group in comparison with the control group. Clearly, the Yater data indicate that elevation both in systolic and diastolic blood pressures characterizes the men in the 18-39 year age group who go on to develop clinical coronary heart disease in comparison with those men of the same age group who remain free of overt clinical coronary heart disease during the same time period.

The combination of the Framingham evidence with Yater's evidence covers the age span for men from 18 to 62 years of age. Over this entire age span the relationship between antecedent blood pressure elevation and later development of clinical coronary heart disease is known to be valid. Yet this is essentially the age span in men for which Master had concluded that there was no "close" relationship between hypertension and the subsequent development of clinical coronary heart disease. No contradiction whatever exists among the findings of Dawber at Framingham, of Yater in the Army, and of Master in his series. All show that blood pressure elevation is associated with a sizably higher attack rate of future clinical coronary heart disease. Master's difficulty resided in his expectation that an *arbitrarily* large percentage of men who subsequently develop clinical coronary heart disease must have a blood pressure elevation of *arbitrary degree* if the blood pressure is to be important. No real justifi-

subjects fit into one or another category, such as borderline hypertension, definite hypertension, and possible or definite hypertensive heart disease. The normotensive group, constituting 310 men, *developed 8 cases of new events classified as manifestations of* clinical coronary heart disease during the four year follow-up period.* The remaining group (various degrees of hypertension by their criteria), constituting 541 men, developed 40 cases of new events classified as manifestations of clinical coronary heart disease during the four year follow-up period. Thus for the "normotensive" group, the incidence rate of de novo clinical coronary heart disease was 26 cases *per 1000 persons at risk over the four year* period, whereas for the "hypertensive" group the incidence rate of de novo clinical coronary heart disease was 74 cases per 1000 persons at risk over the same time period. This difference in attack rates of de novo clinical coronary heart disease is significant and clearly supports the concept that elevation in blood pressure increases the risk of future clinical coronary heart disease. Stated otherwise, this evidence links elevation in blood pressure with the *sub-clinical* phase of coronary heart disease and indicates that the blood pressure is one predictive measure for ascertaining the risk a person carries for passing from the sub-clinical to the clinical phase of coronary heart disease

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*Forty seven of the 898 men were normotensive, but had a history of cerebro vascular accident of rheumatic heart disease These are excluded from analysis

Whatever the merits of this possible explanation for the association of elevation in blood pressure with a higher frequency of clinical coronary heart disease, it has, contrary to many opinions, *no* bearing upon the utility of the blood pressure measurement as a predictive measure in assessing the risk of future clinical coronary heart disease. The data reviewed in this chapter establish conclusively that the average elevation in blood pressure is present *during the sub-clinical* phase of coronary heart disease, and for a period of several years *before* the evolution of clinically-overt coronary heart disease This is the crucial issue with respect to the question of utility of the blood pressure as a *predictive* criterion. Whether the blood pressure is a factor in acceleration of the coronary disease or whether the coronary disease results in the blood pressure rise as a compensatory mechanism, the existence of the pressure elevation during the sub-clinical phase of coronary heart disease *necessarily* means that the measurement of blood pressure is of value in assessing the development of coronary heart disease, and hence the risk of serious future clinical consequences. The possibility of prevention or therapy of coronary heart disease is, of course, a matter apart from such considerations If the blood pressure elevation is truly part of a compensatory mechanism to increase coronary artery blood flow, then efforts to lower blood pressure as a means of preventing or treating coronary heart disease would be unwise. On the other hand if the blood pressure elevation is a predisposing factor to coronary heart disease there would exist excellent justification for attempting to lower the blood pressure in the effort to prevent or treat clinical coronary heart disease. This question cannot be decided from the observation of the association of sub-clinical coronary heart disease with blood pressure elevation Direct clinical preventive and therapeutic experiments are necessary supplements toward this end. However, all the indirect evidence supports the view that the blood pressure elevation accelerates the development of the coronary heart disease rather than that the coronary heart disease causes the elevation in pressure. The experimental animal data point very strongly to the probability that the way in which blood pressure elevation comes to be associated with coronary heart disease is

cation exists for such a view. The extent of the differences in attack rate of clinical coronary heart disease for persons with high blood pressure versus those with low blood pressure is in reality quite phenomenal and provides predictive information of major value. Exactly how these differences are to be utilized in the advance prediction of future clinical coronary heart disease will be detailed in Chapter V.

To be sure, the data from all the sources of evidence show clearly that blood pressure values above some arbitrary high level are not *prerequisite* to the development of clinical coronary heart disease. Clinical coronary heart disease can and does develop in persons with moderate or even low blood pressures, but the frequency of its occurrence is strikingly lower than in persons with elevation in blood pressure. Perhaps another feature which Master found disturbing was that antecedent elevation in blood pressure is much more frequently found in women who develop clinical coronary heart disease than in men who do so. This finding in no way negates the importance of the blood pressure level for the development of clinical coronary heart disease in men at any age. There exist good and sufficient reasons why hypertension should be expected to be a more frequent finding among women who develop clinical coronary heart disease than among men who develop this disease. The explanation of this phenomenon requires consideration of the blood pressure findings together with the lipoprotein findings and the manner in which risk of coronary heart disease is related to both factors operating simultaneously. Therefore detailed consideration of the difference in incidence of hypertension between men and women who develop coronary heart disease is presented in Chapter VIII, where such risk calculations are explained.

There are some, writing on the subject of coronary heart disease, who raise the question as to whether the elevation in blood pressure observed in those who go on more frequently to develop clinical coronary heart disease may not be a protective phenomenon. Thus Yater suggested the possibility that the hypertension which precedes clinical coronary heart disease may be part of an effort to compensate for reduced coronary arterial blood flow by an increase in the pressure in the arterial tree.

viduals at a particular age are evaluated both with respect to lipoprotein levels and blood pressure levels and then followed for a period of years, a sub-group will develop which shows clinically-manifest coronary heart disease. This sub-group, we now know, would have originally been characterized both by elevation in lipoprotein levels and in blood pressure levels. From the extent of correlation of blood lipoprotein levels and blood pressure levels it can be calculated that a certain blood pressure elevation would be expected in the sub-group with clinical coronary heart disease, even if the blood pressure provided *no independent* predictive information. However direct test of such evidence by the author and his colleagues[15] showed that there *is* an elevation of blood pressure *over* and *above* that expected from the correlation of blood lipoproteins and blood pressure. Hence the blood pressure *does* provide information of predictive value concerning future clinical coronary heart disease *in addition* to that provided by lipoprotein analysis An alternative manner of considering the test for independence may be described. If the sub-group which does develop clinical coronary heart disease is matched with random cases from the population-at-large such that the lipoprotein levels are equivalent for both groups, is the blood pressure *still* elevated in the group with clinical coronary disease in comparison with the lipoprotein-matched controls? Direct test of this showed that the blood pressures were still elevated in the coronary disease group even when the two groups were matched upon lipoprotein levels. This is clear evidence that the blood pressure measure provides information additional to, and independent of, that provided by lipoprotein measurement. Hence, in any consideration of risk of future clinical coronary heart disease both factors, blood lipoprotein level and blood pressure level, must be evaluated, or valuable information will necessarily be lost

via the effect of hypertension in acceleration of the coronary arteriosclerotic process. The increased arteriosclerosis in humans in regions of the vascular tree subjected to excessive pressure is consistent with the animal data, and not at all supportive of the concept that the blood pressure elevation is a compensatory phenomenon. Altogether the indirect evidence suggests that the blood pressure elevation, in addition to being predictive of clinical coronary heart disease by virtue of its statistical association with it, in all likelihood abets the development of coronary heart disease.

INDEPENDENCE OF THE INFORMATION PROVIDED BY THE BLOOD PRESSURE

In Chapter III it was shown that conclusive evidence is available to show that the blood low-density lipoproteins are, on the average, elevated during the sub-clinical phase of coronary heart disease, and hence blood lipoprotein measurements have predictive implications for future clinical coronary heart disease. In this chapter it has been shown that similar conclusive evidence is at hand that information of predictive value for clinical coronary heart disease is obtained through the measurement of the blood pressure of persons in advance of any overt manifestations of coronary heart disease. Do these two sets of measurements provide *independent* information concerning the risk of future clinical coronary heart disease? If *no* independent information were provided by blood pressure measurement over and above that provided by lipoprotein measurement, this would mean that any predictive information from blood pressure measurement must have arisen solely through a correlation of elevation of blood pressure with elevation in blood lipoprotein levels In this case the blood pressure measurement would be of no predictive value for future clinical coronary heart disease once the lipoprotein levels were known There does indeed exist a low-order correlation between lipoprotein levels and blood pressure levels. However, this is not sufficient evidence upon which to base the decision as to whether the blood pressure measurement provides *independent* predictive information. The critical test for this point is made in the following manner. If a large group of indi-

develop clinical coronary heart disease in some specified time interval, there simply are not enough data available today to make this sort of exact evaluation. However what information is available makes for a tremendous amount of predictive power, a power that can be used now in a sensible program designed for the prevention of coronary heart disease.

For illustrative purposes in the demonstration of how risk is directly related to the measurement of any particular variable that is elevated in those individuals going on to develop clinical coronary heart disease compared with the population out of which they arise, the data concerning the S_f0-12 lipoprotein measurement in 40-49 year old men will be utilized here. Also because the data are available for a much larger number of cases, the S_f0-12 measurement for a large series of cases with documented clinical coronary heart disease will be used instead of the smaller series of de novo cases of myocardial infarction arising in previous well individuals. This is perfectly justifiable since the levels of the various lipoprotein classes characterizing the de novo cases of myocardial infarction were shown in a previous discussion, (page 57), to be quite comparable with those characterising cases with already-established clinical coronary heart disease. Available also are the distributions of the S_f0-12 lipoproteins in age- and sex-matched controls from the population-at-large. If the coronary cases had arisen out of a large series of such age- and sex-matched controls in overt health, we would have the S_f0-12 distribution of values for the original population sample and the values which characterize those individuals who became cases of clinical coronary heart disease at some future time, whatever that time might be, e.g., 1 year, 2 years or 3 years later. Listed in Table VII is the distribution of S_f0-12 values, assuming a base population of 10,000 subjects evaluated. Actually this distribution was determined on 525 subjects and simply multiplied by a conversion factor to calculate what the numbers would be in each S_f0-12 lipoprotein category for an over-all group of 10,000 subjects. One has, therefore, in Table VII, for each small range of S_f0-12 values, a number which represents the number of individuals found in the population-at-large who would show this S_f0-12 lipoprotein value upon measurement. As is to be expected, most of

Chapter V

THE PREDICTION OF FUTURE CLINICAL CORONARY HEART DISEASE

EVIDENCE is available which indicates conclusively that two independent factors characterize the individual developing excessive *sub-clinical* coronary heart disease. These are the level of certain blood lipoproteins and the level of the diastolic blood pressure. Both for the lipoprotein level and the blood pressure, it has been proven beyond reasonable doubt that the abnormality manifests itself during the sub-clinical phase of coronary disease, namely, before the evolution of the disease into the clinically-overt state. How is this information to be used in the prediction of clinical coronary heart disease risk in otherwise healthy individuals? It can be readily demonstrated through simple arithmetic that, when a measurement (any measurement) shows a higher average value and a shift in the distribution to higher values *for those individuals who later go on to develop clinical* coronary heart disease, such a measurement is directly capable of being translated into a prediction of the risk of future clinical coronary heart disease. At the outset it must be emphasized vigorously that what can be predicted is the *risk* of future clinical coronary heart disease. Much confusion needlessly centers around this point. There is no intent to state or claim that prediction is possible, for a particular individual, that he *will* develop clinical coronary heart disease in any specified time interval. This would not be a risk, but a forecast of future certainty. By risk is meant the probability, or likelihood, of developing coronary heart disease, rather than the certainty involved in naming the day or year a particular individual will develop coronary heart disease. While the physician might like to have unequivocal information concerning whether or not a particular subject will

of our base population for which a risk calculation can be made. If there are 31 cases of coronary disease below the median value arising out of 5000 individuals, this is a coronary disease attack rate of 6.2 per thousand individuals. On the other hand, since there are 82 cases of clinical coronary disease arising out of the 5000 individuals with levels above the median value, this represents an attack rate of 16.4 per thousand, which is 2.65 times as high as the value for the segment of the base population below the median value. Therefore *without any further information* concerning such individuals, it is possible to state that if a person is measured with respect to S_f0-12 lipoprotein level and if his level is above the median value, he is 2.65 times as likely to develop clinical coronary heart disease in some specified time interval as he would be had his S_f0-12 lipoprotein level been below the median value. It is to be remembered that this statement holds when such other variables as age and sex are matched. There is no inference that prediction would be handled in this simple manner if a 20 year old man were to be compared with a 65 year old woman. The problem of dealing with the age and

TABLE VIII

DISTRIBUTION OF S_f0-12 LIPOPROTEIN LEVELS IN 113 CASES OF DOCUMENTED MYOCARDIAL INFARCTION (MEN, AGE 40-49 YEARS)

Range of S_f0-12 Lipoprotein Levels mg/100ml	*Number of Men in Each S_f0-12 Category*
Less than 224	2
224-267	4
268-311	6
312-356	10
357-401	16
402-446	24
447-491	24
492-535	15
536-580	8
581 or higher	4
TOTAL GROUP	113

Median S_f0-12 Lipoprotein Level = 436 mg/100ml

the individuals show values near the median for the S_f0-12 lipoprotein level for 40-49 year old males (average age = 44.5 years), which is 381 mg/100ml. Listed in Table VIII is the corresponding distribution of S_f0-12 lipoprotein levels for the 113 cases of clinical myocardial infarction which can be said to have developed out of a population comparable to that shown in Table VII in a time period such as two to three years. The simplest approach to translation of these two tables of values into predictive terms would be to consider values above and below the median value of the S_f0-12 lipoproteins for the base population. For this base population of 10,000 persons the definition of the median value implies that there will be 5000 individuals with S_f0-12 lipoprotein levels above that value and 5,000 individuals with levels below that median value. If we now direct attention to the cases of myocardial infarction arising out of such a base population and total up the number of cases below this same median value of 381 mg.%, we find there are 31 values below this level and 82 values above this level. Therefore we have a two-fold split

TABLE VII

DISTRIBUTION OF S_f0-12 LIPOPROTEIN LEVELS IN AN OVERTLY HEALTHY BASE POPULATION OF 10 000 MEN (AGE 40-49 YEARS)

Range of S_f0-12 Lipoprotein Levels (mg/100ml)	*Number of Men in Each S_f0-12 Category*
Less than 224	362
224-267	476
268-311	1143
312-356	1791
357-401	2115
402-446	1980
447-491	1372
492-535	514
536-580	171
581 or higher	76
TOTAL GROUP	10,000

Median S_f0-12 Lipoprotein Level = 381 mg/100ml
S_f0-12 Level separating lowest from second lowest quarter of group = 327 mg/100ml
S_f0-12 Level separating third quarter from highest quarter of group = 439 mg/100ml

process further allows the construction of a table of 10 individual categories relating risk of future clinical coronary heart disease to S_f0-12 lipoprotein levels. Such a risk evaluation for various S_f0-12 lipoprotein levels is presented in Table IX, where the risk for the lowest S_f0-12 level is arbitrarily set at 1.0, and where all other risk values are expressed in comparison with this value. Without any further information about the persons involved, such a table can be used to determine the relative risk of one individual versus another developing future clinical coronary heart disease in a specified time interval Many misleading statements have emanated from some writers, who have stated that this type of risk information holds true for groups but does not apply to the individual. Such reasoning is entirely erroneous. A *risk* is a value that has meaning *for an individual.* The error arises from the fact that some persons are confusing the *risk* of future clinical coronary heart disease with an absolute statement of the day, week, or month that this particular individual will develop clinical coronary heart disease. Let us review what is meant by risk. Suppose that two groups, each constituting one thousand individuals, are considered, the first group all having S_f0-12 lipoprotein levels of 200 mg/100ml and the second group

TABLE IX

RELATIVE RISK OF MYOCARDIAL INFARCTION AT VARIOUS S_f0 12 LIPOPROTEIN LEVELS

S_f0 12 Lipoprotein Level (in mg/100ml)	*Relative Risk of Development of Myocardial Infarction (All risks referred to the risk at 200 mg/100ml S_f0-12 lipoproteins set at 1.00)*
200	1 00
250	1 06
300	1 15
350	1.22
400	1.50
450	2 30
500	3 90
550	6.30
600	9 75
650	13.2

the sex factors will be considered later (Chapters VII and VIII).

It is quite evident that such a two-fold prediction table can readily be extended. There is no reason to limit sub-division of the base population with respect to standard S_f0-12 level to just a two-fold split above and below the median value. The base population can be sub-divided still further into the lowest quarter, the next quarter, the third quarter, and the highest quarter of the group of individuals with respect to S_f0-12 levels, yielding 2500 individuals in each of the four categories. The S_f0-12 lipoprotein level that separates the lowest quarter from the second lowest quarter is 327 mg/100ml, the level that separates the third quarter from the highest quarter is 439 mg/100ml, and the median value, 381 mg/100ml separates the two intermediary quarters. From the overall group of cases of coronary disease, those with S_f0-12 lipoprotein levels below the value separating the lowest quarter from the second lowest quarter come to 14 cases. In the second lowest quarter there are 17 cases, in the third quarter there are 25 cases, and in the highest quarter there are 57 cases. Now it is possible to compare the risk of future clinical coronary heart disease for individuals in any one quarter with the risk for individuals in any other quarter. If, in the lowest quarter, there are 14 cases arising out of 2500 people, then the coronary disease attack rate is 5.6 cases per thousand persons at risk, for the second quarter the rate is 6 8 per thousand, for the third quarter the rate is 10.0 per thousand, and for the highest quarter the rate is 22.8 per thousand. Comparison of the attack rate for any quarter with that for any other quarter provides immediately the relative risk of future clinical coronary heart disease carried by persons in these categories simply on the basis of S_f0-12 lipoprotein levels.

It is quite evident that, with respect to the S_f0-12 lipoprotein measurement, the base population could have been subdivided into ten segments, each representing an interval of S_f0-12 lipoprotein levels from the lowest ten percent of the population up through to the highest ten percent. Then by counting the number of cases of clinical coronary disease in each such segment, calculation of the number of cases per thousand persons at risk for each segment is readily possible. Carrying such a

process further allows the construction of a table of 10 individual categories relating risk of future clinical coronary heart disease to S_f0-12 lipoprotein levels. Such a risk evaluation for various S_f0-12 lipoprotein levels is presented in Table IX, where the risk for the lowest S_f0-12 level is arbitrarily set at 1.0, and where all other risk values are expressed in comparison with this value. Without any further information about the persons involved, such a table can be used to determine the relative risk of one individual versus another developing future clinical coronary heart disease in a specified time interval. Many misleading statements have emanated from some writers, who have stated that this type of risk information holds true for groups but does not apply to the individual. Such reasoning is entirely erroneous. A *risk* is a value that has meaning *for an individual.* The error arises from the fact that some persons are confusing the *risk* of future clinical coronary heart disease with an absolute statement of the day, week, or month that this particular individual will develop clinical coronary heart disease. Let us review what is meant by risk. Suppose that two groups, each constituting one thousand individuals, are considered, the first group all having S_f0-12 lipoprotein levels of 200 mg/100ml and the second group

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200	1.00
250	1 06
300	1 15
350	1.22
400	1.50
450	2 30
500	3 90
550	6.30
600	9 75
650	13.2

all having S_f0-12 lipoprotein levels of 500 mg/100ml. The data in Table IX indicate that the relative risk of future coronary heart disease for members of the high group is 3.90 times that of the low group. What this means is that if the 1000 individuals with low S_f0-12 lipoprotein values and the thousand individuals with the high S_f0-12 values were in apparent clinical health (which means that they are in the sub-clinical phase of coronary heart disease) and if both groups were observed for a time period such as two years, clinical coronary heart disease would develop in some members of both groups. If, out of the thousand individuals with the lowest S_f0-12 levels, there developed 10 cases of clinical coronary heart disease, then the relative risk table means that out of the group of 1000 individuals with the high S_f0-12 levels there would be 3.90 times ten, or 39 cases of clinical coronary heart disease. Obviously it is true that even for the group with high lipoprotein levels *most* individuals do not develop *clinical* coronary heart disease in a short specified time interval such as two years, but this represents no erroneous diagnosis of the *risk* for such persons. No false assessment of a person's chance of development of coronary heart disease is represented by this fact. It is simply inherent in the nature of a risk calculation that many persons will escape the disease even though they are individually characterized by a very high risk of such disease compared with other persons.

In an entirely analogous manner one could treat the S_f12-20 lipoprotein measurement to calculate a coronary heart disease risk value that corresponds with each and every level of the S_f12-20 lipoproteins, without any consideration of any other lipoprotein classes or blood pressure, provided considerations are limited to age- and sex-matched individuals Further, one could separately calculate a table for S_f20-100 lipoprotein level versus risk of clinical coronary heart disease and for S_f100-400 lipoprotein level versus risk of such disease. Additionally, similar risk calculations could readily be made for the diastolic blood pressure alone in a fashion exactly analogous to that outlined in detail for the S_f0-12 lipoproteins. Proceeding in this manner, one would have five separate measurements and five separate risk calculations concerning an individual. A particular person might be

twice as high as the average in terms of risk of coronary heart disease because of his S_f0-12 lipoprotein level but might be four times as high as the average because of his S_f12-20 lipoprotein level, etc Clearly, having five separate risk values to consider without a method for weighing the relative importance of each of these separate risk estimates would be very unwieldy and difficult to handle in clinical practice. Therefore it is necessary to weld the separate sources of risk information together into some composite measures which best express the overall relative risks of any two individuals with respect to the development of future clinical coronary heart disease This problem may be approached in two stages, first, to unify all the lipoprotein risk calculations, namely, to get together in one composite measure of risk that information that derives from S_f0-12, 12-20, 20-100 and 100-400 lipoprotein measurements, and second, to evaluate the risk separately arising from blood pressure values. Finally, it is essential to combine these two risk evaluations into a single composite risk estimate which takes into account all the available information. It is important to re-emphasize here that the reason why all the four separate lipoprotein classes must be taken into account is that each class provides information independent of all the others with respect to coronary disease risk Each class of lipoproteins is involved in the progression of sub-clinical coronary heart disease and hence contributes to the risk of ultimate clinical coronary heart disease If knowledge of the level of one lipoprotein class provided the level of the others, then measurement of any one of the lipoprotein classes would suffice for present purposes. However, it is well-known that a person may be high in S_f0-12 lipoproteins but low in all the other three lipoprotein classes, whereas some other person may be equally high in S_f0-12 lipoproteins and high in one or more of the other three classes. The latter person carries a higher risk of future clinical coronary disease than does the former The human population is so constituted that practically any combination of S_f0-12, 12-20, 20-100 and 100-400 lipoproteins is possible and does occur. Hence the best evaluation of a person with respect to the risk of future clinical coronary heart disease is to be obtained by a combination of the evaluation that derives from each of the four classes sep

all having S_f0-12 lipoprotein levels of 500 mg/100ml. The data in Table IX indicate that the relative risk of future coronary heart disease for members of the high group is 3.90 times that of the low group. What this means is that if the 1000 individuals with low S_f0-12 lipoprotein values and the thousand individuals with the high S_f0-12 values were in apparent clinical health (which means that they are in the sub-clinical phase of coronary heart disease) and if both groups were observed for a time period such as two years, clinical coronary heart disease would develop in some members of both groups. If, out of the thousand individuals with the lowest S_f0-12 levels, there developed 10 cases of clinical coronary heart disease, then the relative risk table means that out of the group of 1000 individuals with the high S_f0-12 levels there would be 3.90 times ten, or 39 cases of clinical coronary heart disease. Obviously it is true that even for the group with high lipoprotein levels *most* individuals do not develop clinical coronary heart disease in a short specified time interval such as two years, but this represents no erroneous diagnosis of the *risk* for such persons. No false assessment of a person's chance of development of coronary heart disease is represented by *this fact. It is simply inherent in the nature of a risk calculation* that many persons will escape the diśease even though they are individually characterized by a very high risk of such disease compared with other persons.

In an entirely analogous manner one could treat the S_f12-20 lipoprotein measurement to calculate a coronary heart disease risk value that corresponds with each and every level of the S_f12-20 lipoproteins, without any consideration of any other lipoprotein classes or blood pressure, provided considerations are limited to age- and sex-matched individuals. Further, one could separately calculate a table for S_f20-100 lipoprotein level versus risk of clinical coronary heart disease and for S_f100-400 lipoprotein level versus risk of such disease. Additionally, similar risk calculations could readily be made for the diastolic blood pressure alone in a fashion exactly analogous to that outlined in detail for the S_f0-12 lipoproteins Proceeding in this manner, one would have five separate measurements and five separate risk calculations concerning an individual. A particular person might be

100 cases, where the mean value of each lipoprotein class is not as stabilized as it would be with a much larger series of cases, the precise value of the weighting factors is not stably evaluated. It is to be anticipated that the weighting factor determined for each class might fluctuate if studied in one series versus another and might fluctuate some as additional cases are added to the overall series. Because of this sensitivity of the weighting factor to the exact difference in mean value for any lipoprotein class in the coronary and non-coronary cases, it was decided to reduce this sensitivity by combining the S_f12-20 plus S_f20-100 plus S_f100-400 lipoproteins into one composite band and to derive a weighting factor for this band relative to the S_f0-12 band of lipoproteins as a first step. At some future time it will be desirable to have specific weighting factors for each of the lipoprotein sub-classes, but for the present, within the limits imposed by the size of the series of cases studied, it has been decided not to attempt to determine the weighting factor for all the separate bands. The application of the analysis of Fisher to coronary disease cases in men of the age range of 40-59 years had led to a weighting factor for the S_f12-400 band of lipoproteins of approximately 1.75 times that for the S_f0-12 lipoproteins[31]. Therefore, instead of combining the S_f0-12 lipoprotein measurement directly with the S_f12-400 lipoprotein measurement to obtain a *composite* value, one should first multiply the number of milligrams per 100 ml of S_f12-400 lipoproteins by 1.75 before adding it to the number of milligrams per 100 ml of S_f0-12 lipoproteins. In order to reduce the composite values obtained to a composite value of convenient dimensions, all values are arbitrarily divided by ten. (This is really equivalent to use of centigrams per 100 ml instead of milligrams per 100 ml) This composite value of the S_f0-12 lipoprotein level plus 1.75 times the S_f12-400 lipoprotein level had been designated as an *Atherogenic Index, or A.I. value*[31]. This A.I. value *need imply nothing* with respect to arteriosclerosis or atherogenesis, but simply is a composite value expressive of the weighted importance assigned to each of the lipoprotein classes with respect to coronary heart disease. To be sure, the name, A.I. value, or Atherogenic Index value, was chosen because it was strongly surmised that it had to do with atherogenesis

arately. If each lipoprotein class were exactly equal in importance with respect to the development of coronary heart disease, that is, if one milligram percent of S_f0-12 lipoproteins were equivalent in its effect to one milligram percent of S_f12-20, or one milligram percent of S_f20-100, or one milligram percent of S_f100-400 lipoproteins, there would be a very simple procedure available for rating an individual. Simple addition of the values for the S_f0-12, 12-20, 20-100 and 100-400 lipoprotein levels to yield the S_f0-400 level could be performed. Then in a manner similar to that described above for the S_f0-12 lipoproteins the risk of future coronary heart disease as related to the S_f0-400 level could be calculated. This simplest approach of assuming that each milligram percent of every lipoprotein class means the same thing as each milligram percent of any other lipoprotein class would be certainly a step in the right direction for producing a composite risk estimate. However, there exist methods for treating this problem a little more critically instead of *assuming that each milligram percent of a particular lipoprotein class is* equivalent to one milligram percent of any other class with respect to coronary heart disease. The British statistician, Fisher[30], has developed a statistical method for dealing with problems such as this, which allows calculation of a weighting factor to be applied to each of the measurements before adding the separate measurements. For example, should Fisher's method indicate that S_f12-20 lipoproteins deserve a weighting factor of 2 compared with a weighting factor of 1 for S_f0-12 lipoproteins, that S_f20-100 lipoproteins deserve a weighting factor of 2½, and that S_f100-400 lipoproteins, a weighting factor of 3, then instead of adding together the milligrams percent directly, one would add the milligrams percent of S_f0-12 plus 2 times the milligrams percent of S_f12-20 plus 2½ times the milligrams percent of S_f20-100 plus 3 times the milligrams percent of S_f100-400 to obtain a composite value that best characterizes the individual. The precise values of the weighting factors for each lipoprotein class are *somewhat sensitive to the magnitude of the difference* in average lipoprotein levels between coronary disease and non-coronary disease cases for each of the lipoprotein classes. Therefore with a small series of cases of coronary disease, even a series of

the S_f0-12 lipoproteins. The Atherogenic Index value, or A.I. value, is calculated for each person from his lipoprotein levels. This can be done for the base population of 10,000 (40-49 year old) men in apparent health as discussed previously and can be done for a series of coronary disease cases that would in time grow out of such a base population. The persons in both the original healthy series and the clinical coronary disease series can be ranked in ten categories, from the Atherogenic Index values for the lowest 10% of the healthy group up through the values for the highest 10% of the healthy group. These values are categorized in Tables X and XI From these data the number of coronary disease cases per 1000 healthy persons in each Atherogenic Index category is immediately available. The ratio of the number of coronary disease cases per thousand healthy men for any two Atherogenic Index categories is *directly* the relative risk of clinical coronary heart disease for these categories. Such relative risks are presented in Table XII.

The Atherogenic Index composite risk calculation takes into account all the information from the various lipoprotein measurements, but does not take into account the blood pressure information The blood pressure will be considered below. At the moment consideration must be given to the problem of how

TABLE X

RANGES OF ATHEROGENIC INDEX VALUES EACH COMPRISING 1000 MEN OUT OF A BASE POPULATION OF 10 000 OVERTLY HEALTHY MEN (AGE 40-49 YEARS)

Atherogenic Index Categories Each Containing 1000 Men	*Range of Atherogenic Index Values*
Lowest category of 1000 men	Below 48
2nd category of 1000 men	49 55
3rd category of 1000 men	56-61
4th category of 1000 men	62-67
5th category of 1000 men	68 73
6th category of 1000 men	74 78
7th category of 1000 men	79 87
8th category of 1000 men	88 96
9th category of 1000 men	97 108
Highest category of 1000 men	Above 109

in the coronary arteries. However, since this entire thesis is being developed without any need to refer to atherogenesis, the A.I. value can *simply be defined* as the S_f0-12 lipoprotein level plus 1.75 times the S_f12-400 lipoprotein level. As an illustration of the calculation of Atherogenic Index values, the following example is considered. If a person shows 365 mg/100ml of S_f0-12 lipoproteins and 150 mg/100ml of S_f12-400 lipoproteins, the Atherogenic Index value will be equal to 365 plus 1.75 times the 150, all divided by ten, which yields an A.I. value of 63 units. Such a composite value is a step closer to the best composite value than that obtained by simply adding all the lipoprotein measurements together because it takes into account the weighted importance of the S_f12-400 lipoproteins. It is to be anticipated that when a larger series of coronary disease cases is studied, and especially when a large series has arisen out of an original base population of individuals, and the mean difference for each of the lipoprotein classes is fixed more precisely for the coronary disease cases versus the matched controls, the weighting factor of 1.75 for the S_f12-400 lipoproteins versus 1.0 for the S_f0-12 lipoproteins may change some. It may go down from 1.75 or it may go up some. However none of the conclusions derived from utilization of the 1.75 value will be appreciably altered by such a shift in the value. The crucial issue to understand is that, since a person derives his risk of future clinical coronary disease from all four classes of lipoproteins S_f0-12, S_f12-20, S_f20-100, and S_f100-400), they must *all* be considered. For the present time the best weighting factor for S_f12-400 lipoproteins appears to be approximately 1.75 times that for the S_f0-12 lipoproteins, but the composite value derived thereby is not critically affected for clinical purposes should the weighting factor finally need minor revision upward or downward.

The availability of the composite Atherogenic Index value which takes *all* the lipoprotein information into account makes it possible to evaluate the risk of future clinical coronary heart disease with complete lipoprotein information for each case rather than with just the S_f0-12 lipoprotein levels as was developed for illustrative purposes earlier in this chapter. The procedure for such risk evaluation is precisely that which was employed with

TABLE XII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (40-49 YEAR OLD MEN)

(Uncorrected for association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1.06
40	1.13
45	1.20
50	1.33
55	1.60
60	2.13
65	2.66
70	3.40
75	4.53
80	6.20
85	8.06
90	10.1
95	12.7
100	15.6
105	19.0
110	23.2

THE RISK OF CORONARY HEART DISEASE ARISING FROM DIASTOLIC BLOOD PRESSURE

In the immediately preceding discussion the problem of calculating the risk of clinical coronary heart disease by measurement of the Atherogenic Index alone has been elaborated. These calculations are correct of and by themselves. If this were all that could be done with the prediction problem, it would represent a great step ahead of no knowledge at all. However in Chapter IV it was demonstrated that the blood pressure is a factor independent of the lipoprotein levels in determining the risk of clinical coronary heart disease. Therefore it should be possible to improve the segregation of individuals with respect to their risk of future clinical coronary heart disease by taking into

TABLE XI

DISTRIBUTION OF 113 MYOCARDIAL INFARCTION CASES INTO THOSE RANGES OF ATHEROGENIC INDEX VALUES WHICH SEGREGATE THE HEALTHY POPULATION INTO GROUPS EACH CONTAINING 10% OF TOTAL GROUP

Atherogenic Index Ranges for Each Category (Units)	*Number of Myocardial Infarction Cases in each Atherogenic Index Range*
48 and below	2
49-55	2
56-61	3
62 67	4
68-73	5
74-78	7
79-87	11
88-96	18
97-108	25
109 and above	36
Total Number of Cases	113

long in advance of occurrence of clinical coronary heart disease the prediction of relative risk based upon the Atherogenic Index is valid. Precisely the same considerations hold for the Atherogenic Index as held for the lipoprotein measurements out of which it is derived since it is simply a composite measure expressing the information contained in the lipoprotein measurements. In the previous discussion (Chapter III) it was shown that the lipoprotein elevation occurs in advance of clinical coronary heart disease by at least one to three years. It was indicated further, from the study of population trends and the study of individuals, that persons with high lipoprotein values, and hence high Atherogenic Index values, remain high whereas those who are low remain low during most of adult life. Therefore the period of one to three years of predictive value may in all likelihood be extended to 5, 10, 15 or even 20 years before the occurrence of clinical heart disease.

values is directly a measure of *risk* of myocardial infarction for that particular blood pressure range. These data then can be used to construct a table of risk, in terms of the number of infarction cases per 1000 persons at risk at successive blood pressure values. By setting this risk equal to 1.0 at some arbitrary diastolic pressure value, e g, 50 mm Hg, the risks for all other blood pressure values can be expressed *relative* to the risk at 50 mm Hg. This set of relative risks of myocardial infarction for various diastolic blood pressure values is presented in Table XIII Thus, wholly independent of any of the lipoprotein information, the relative risk of clinical coronary heart disease has been calculated for various diastolic blood pressure values If the lipoprotein levels were wholly unrelated to blood pressures the calculation of the risk due to elevation of blood pressure could be immediately superimposed upon the risk due to the blood lipoproteins However, there is a weak correlation of Atherogenic Index values with blood pressure levels, meaning that in the population-at-large as the Atherogenic Index rises there is anticipated a slight rise in average blood pressure levels and conversely as the diastolic blood pressure rises, there is anticipated a slight rise in the average Atherogenic Index value. Therefore, a small part of the *increased* risk of clinical coronary heart disease at a particular elevated Atherogenic Index value is the result of the increased blood pressure which, on the average, is associated with that elevation in Atherogenic Index value. Since this rise in blood pressure level with Atherogenic Index is known, the table of risk versus Atherogenic Index can be corrected for the risk rise occasioned by the average rise in blood pressure which accompanies the rise in Atherogenic Index. In Table XIV (a) is presented the risk versus Atherogenic Index data, corrected for the association of blood pressure with Atherogenic Index

The rise in average Atherogenic Index value with rise in diastolic blood pressure value in the population-at-large is also significant, especially at blood pressures above 70 mm Hg. For diastolic blood pressures below 70 mm Hg, there is almost no detectable change of average Atherogenic Index value with change in blood pressure. Above 70 mm Hg, there is approxi-

account the blood pressure levels as well as the Atherogenic Index values. How is this to be done? In precisely the same fashion as was done for the Atherogenic Index, a population sample of 10,000 men can be divided into 10 sub-segments each containing 1000 men ranked upon diastolic blood pressure values. It is known from data such as those of Yater and co-workers what the distribution of diastolic blood pressure values would be for a group of myocardial infarction cases that would arise out of such a base population of 10,000 men. Therefore the number of myocardial infarction cases for each blood pressure range containing 1000 of the men of the original base population is available from the Yater data. The number of myocardial infarction cases per 1000 men for each range of diastolic blood pressure

TABLE XIII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION AT VARIOUS DIASTOLIC BLOOD PRESSURE VALUES (MALES)

(Uncorrected for association of Atherogenic Index values with Diastolic Blood Pressure)

Diastolic Blood Pressure mm Hg	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 50 mm Hg)*
50	1.00
55	1.11
60	1.28
65	1.72
70	2.89
75	5.11
80	7.33
85	9.66
90	12.4
95	15.7
100	19.2
105	22.5
110	26.2
115	30.2
120	34.6
130	39.1
140	41.6
150	50.2

But since the relationship of Atherogenic Index with relative risk of myocardial infarction is available (Table XII) it is readily possible to correct the blood pressure risks for the rise in Atherogenic Index with rise in blood pressure. This is illustrated as follows: At a blood pressure of 50 mm Hg the average Atherogenic Index value for 30-39 year old men is 66.0 units, whereas for a blood pressure of 90 mm of Hg, the average Atherogenic Index is 70.6 units. Such a rise in Atherogenic Index itself raises the risk of myocardial infarction. From Table XII this relative risk for 70.6 A.I. units is approximately 1.24 times that

TABLE XIV(b)

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION AT VARIOUS DIASTOLIC BLOOD PRESSURE VALUES (MALES)

*(Corrected for association of Atherogenic Index values with Diastolic Blood Pressure)**

Diastolic Blood Pressure mm Hg	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 50 mm Hg)*
50	1.00
55	1.02
60	1.09
65	1.32
70	2.01
75	3.23
80	4.16
85	4.98
90	5.79
95	6.68
100	7.53
105	8.06
110	8.70
115	9.32
120	9.82
130	10.8
140	11.7
150	12.5

*Each value in this table [illegible]
association [illegible]
data of Tab[illegible]
was made b[illegible]

mately a 2.4 unit rise in Atherogenic Index for a 10 mm Hg rise in diastolic pressure. When the relative risk of myocardial infarction versus diastolic pressure is estimated directly from blood pressure distributions for persons in health and for the myocardial infarction cases that grow out of a healthy population, *part* of the increased risk with increased blood pressure is really the result of the rise in Atherogenic Index with rise in pressure.

TABLE XIV (a)

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (40-49 YEAR OLD MEN)

*(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)**

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1 05
40	1.10
45	1 15
50	1.27
55	1.48
60	1.92
65	2 35
70	2 93
75	3 81
80	5 17
85	6 61
90	8.15
95	9 92
100	11 7
105	14 1
110	16 8
115	19 8
120	23.1
125	26 7
130	30 6

* [illegible] of Table XII for the [illegible] value utilizing the [illegible] mplete correction,

from the blood pressure. Such combination is readily possible if one approximation is made, an approximation that is almost certain to be an excellent one. This approximation is that if a particular elevation in Atherogenic Index value multiplies the coronary disease risk by a certain factor for persons all of whom have one particular blood pressure value, it multiplies the risk by the same factor for persons all of whom have some other blood pressure value. An illustration of this approximation follows: Our previous calculations indicate that the risk of future coronary disease doubles for an increase in Atherogenic Index value from 50 units to 65 units in 40-49 year old men (see Table XII). The approximation being made is that this would hold true if two men were being compared both of whom had diastolic blood pressures of 70 mm Hg, or if both of whom had some other diastolic pressure such as 80 mm, 90 mm or 100 mm Hg. The analogous approximation is made that if a particular elevation in diastolic blood pressure multiplies the coronary disease risk a certain amount for persons all of whom have one particular Atherogenic Index value, it multiplies the risk by the same factor for persons all of whom have some other Atherogenic Index value If either of these approximations deviates from actuality at all, it is extremely doubtful that any such deviation will be appreciable relative to the risk factors that will apply in the comparison of various persons

The combination of the future coronary heart disease risk from blood pressure measurement with that from Atherogenic Index values now becomes simplified Let us set the relative risk for the 45 year-old man who is characterized by an Atherogenic Index value of 30 units and a diastolic blood pressure value of 50 mm Hg at 1 0 (On a *relative* scale the risk of a person can be arbitrarily set at 1 0 for some convenient set of Atherogenic Index and diastolic pressure values) Now, if a 45 year old man whose Atherogenic Index is 85 units and whose diastolic blood pressure is 75 mm Hg is considered, how does he rate compared with the first man with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg? From Table XIV (a) the corrected relative risk in passing from an Atherogenic Index value of 30 units to 85 units is 6 61 times as high. Now since this is the

for 66.0 A.I. units. Therefore, an excellent correction of the relative risk of myocardial infarction for a blood pressure of 90 mm Hg versus that for a blood pressure of 50 mm Hg is achieved by multiplying that relative risk by 1/1.24, or 0.81. When this is done, the relative risk for the two pressures no longer has within it that increment in risk due to the Atherogenic Index elevation which goes with the blood pressure elevation. In Table XIII the relative risk for a blood pressure of 90 mm Hg is listed as 12.4 times that for a blood pressure of 50 mm Hg. Multiplying 12.4 by 0.81 yields 10.0, which is the relative risk for a blood pressure of 90 mm Hg compared with that for 50 mm Hg *after removal* of the increase in relative risk which results from the association of Atherogenic Index values with blood pressure levels. The relative risk of myocardial infarction for every diastolic blood pressure value can be corrected in an entirely analogous manner. In Table XIV (b) are presented the risk versus diastolic pressure values corrected for the effect of the association of rising average Atherogenic Index with rising blood pressure. Therefore, these corrected risks of myocardial infarction for each blood pressure value are free of the effects of Atherogenic Index alteration. *It is this corrected table of relative risks associated with various blood pressure values that must be used in all subsequent calculation of overall risk of myocardial infarction.*

COMBINATION OF ESTIMATES OF RISK OF MYOCARDIAL INFARCTION TO OBTAIN OVERALL RISK

Medical interest centers about the *overall ranking* of apparently healthy individuals with respect to the chance, or risk, of development of future clinical coronary heart disease. Since risk rises with increasing Atherogenic Index values and independently with increasing diastolic blood pressure values, it is evident that the overall risk of a person with *elevation in both these* factors must be higher than that for a person with an equivalent elevation only in *one* of the two factors. It is essential, therefore, that some practical method be developed to combine the risks estimated separately from the Atherogenic Index value and

The *overall risk* is therefore 16.8x7.53 or 126.5 times that of a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg.

Similarly, for Case (*b*):

From Atherogenic Index, the relative risk is 1.10 times that for an Atherogenic Index of 30 units.

From diastolic pressure, the relative risk is 7.53 times that for a diastolic pressure of 50 mm Hg.

The *overall risk* is 1.10x7.53, or 8.28 times that of a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

For Case (*c*):

From Atherogenic Index, the relative risk is 16.8 times that for an Atherogenic Index of 30 units.

From diastolic pressure, the relative risk is 1.09 times that for a diastolic pressure of 50 mm Hg

The *overall risk* is 16.8x1.09, or 18.3 times that for a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

For Case (*d*):

From Atherogenic Index, the relative risk is 1.10 times that for an Atherogenic Index of 30 units.

From diastolic pressure, the relative risk is 1.09 times that for a diastolic pressure of 50 mm Hg.

The *overall risk* is 1.10x1.09, or 1.20 times that for a person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg

With these calculated risks, any two of these men can now be directly compared with respect to *overall risk* of coronary heart disease The man with the highest risk (Case (a)) has 126.5 times the risk of the person with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg. The man with the lowest risk (Case (d)) has 1.20 times the risk of a person with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg. The comparison of Case (a) and Case (d) is made by comparing 126.5 with 1.20. Therefore Case (a) has 126.5/1.20, or 105.4 times the coronary [illegible] risk of Case

increase in risk for the Atherogenic Index change without change in blood pressure, it is now appropriate to consider the risk rise for the blood pressure increase, holding the Atherogenic Index constant. In Table XIV (b) it is shown that a diastolic blood pressure rise from 50 mm Hg to 75 mm Hg corresponds to a relative risk of 3.23 times. *The overall risk of coronary heart disease is obtained by multiplication of that arising from the Atherogenic Index by that arising from the blood pressure.* Therefore, multiplying 6.61x3.23 one obtains 21.4. Therefore, the net, or overall, risk of this person is 21.4 times that of the person with an Atherogenic Index of 30 units and a blood pressure of 50 mm Hg. Thus to compare the coronary disease risk of any person of this age with that for any other person it is simply necessary to multiply together the separate factors for increase or decrease in risk with the change of Atherogenic Index and the change in blood pressure, respectively. Since relative risk was set at 1.0 for an Atherogenic Index of 30 units and a blood pressure of 50 mm, all persons should have their risks calculated with respect to these reference points, and then after multiplying the Atherogenic Index risk by the blood pressure risk, the overall risk thereby obtained may be compared directly for the individuals concerned. This procedure is illustrated below, with consideration of four types of cases:

Case (a) A man 45 years of age with a high diastolic blood pressure (100 mm Hg) and a high Atherogenic Index value (110 units)

Case (b) A man 45 years of age with a high diastolic pressure (100 mm Hg) and a low Atherogenic Index value (40 units)

Case (c) A man 45 years of age with a low diastolic pressure (60 mm Hg) and a high Atherogenic Index (110 units).

Case (d) A man 45 years of age with a low diastolic pressure (60 mm Hg) and a low Atherogenic Index value (40 units)

For Case (a):

From Table XIV (a) the relative coronary disease risk (for Atherogenic Index) is 16.8 times that of a person with an Atherogenic Index of 30 units.

From Table XIV (b), the relative coronary disease risk (for blood pressure alone) is 7.53 times that for a person with a diastolic pressure of 50 mm.

cases with Case (d); they can be directly compared. Thus Case (b) has 8.28/18.3 = 0.45 times the risk of Case (c). This last intercomparison illustrates how the effect of a high Atherogenic Index can be offset by the effect of a low diastolic blood pressure, and vice versa. *Overall risk* evaluation demands consideration of both Atherogenic Index and blood pressure.

The illustrative examples above of calculation of overall risk of coronary heart disease were for the intercomparison of 40-49 year old men. Similar calculations are, of course, of interest to the clinician for the intercomparison of 30-39 year old men with each other, of 50-59 year old men with each other, and of 60-69

TABLE XVI

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (50-59 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.22
55	1.32
60	1.58
65	1.99
70	2.59
75	3.25
80	4.17
85	5.02
90	5.91
95	6.81
100	7.71
105	8.81
110	10.0
115	11.2
120	12.8
125	14.3
130	16.0

(d). This, it is seen, is a relatively enormous segregation of these two cases upon coronary heart disease risk, based upon the two measurements, Atherogenic Index and blood pressure. Cases (b) and (c) have intermediary values of the *overall risk*, Case (b) having a risk of 8.28/1.20, or 6.9 times that of Case (d), and Case (c) having a risk of 18.3/1.20 or 15.3 times that of Case (d). It is of course not necessary to compare all the other

TABLE XV

Relative Risk of Development of Myocardial Infarction for Various Atherogenic Index Values (30-39 Year Old Men)

(Corrected for association of diastolic blood pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30)*
30	1.00
35	1.24
40	1.46
45	1.68
50	1.90
55	2.20
60	2.59
65	3.10
70	3.78
75	4.97
80	6.46
85	8.20
90	10.2
95	12.0
100	13.8
105	16.0
110	18.8
115	22.2
120	26.3
125	30.4
130	35.3
135	40.1
140	45.0
145	50.6
150	55.6

cases with Case (d); they can be directly compared. Thus Case (b) has 8.28/18.3 = 0.45 times the risk of Case (c). This last intercomparison illustrates how the effect of a high Atherogenic Index can be offset by the effect of a low diastolic blood pressure, and vice versa. *Overall risk* evaluation demands consideration of both Atherogenic Index and blood pressure.

The illustrative examples above of calculation of overall risk of coronary heart disease were for the intercomparison of 40-49 year old men. Similar calculations are, of course, of interest to the clinician for the intercomparison of 30-39 year old men with each other, of 50-59 year old men with each other, and of 60-69

TABLE XVI

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (50-59 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.22
55	1.32
60	1.58
65	1.99
70	2.59
75	3.25
80	4.17
85	5.02
90	5.91
95	6.84
100	7.74
105	8.81
110	10.0
115	11.2
120	12.8
125	14.3
130	16.0

(d). This, it is seen, is a relatively enormous segregation of these two cases upon coronary heart disease risk, based upon the two measurements, Atherogenic Index and blood pressure. Cases (b) and (c) have intermediary values of the *overall risk*, Case (b) having a risk of 8.28/1.20, or 6.9 times that of Case (d), and Case (c) having a risk of 18.3/1.20 or 15.3 times that of Case (d). It is of course not necessary to compare all the other

TABLE XV

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (30-39 YEAR OLD MEN)

(Corrected for association of diastolic blood pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30)*
30	1.00
35	1.24
40	1.46
45	1.68
50	1.90
55	2.20
60	2.59
65	3.10
70	3.78
75	4.97
80	6.46
85	8.20
90	10.2
95	12.0
100	13.8
105	16.0
110	18.8
115	22.2
120	26.3
125	30.4
130	35.3
135	40.1
140	45.0
145	50.6
150	55.6

genic Index data. These tables are to be used for calculations of relative risk within each age decade just as in the illustrative examples above for 40-49 year old men.

THE PROBLEM OF AGE IN THE PREDICTION OF FUTURE CLINICAL CORONARY HEART DISEASE

Since all the development of overall risk estimates of future coronary heart disease was carried through holding age bracket constant, such risk estimates are appropriate to compare a particular man of *one* age, e.g., 44 years, with another man also 44 years of age. Stretching the estimates one can without appreciable error compare two men in the same age decade, e.g., 40-49 years, even though they differ in age by a couple of years. However, it would *not* be appropriate to use such risk tables directly to compare a 35 year old man with a 65 year old man. Nor would it be permissible to use these tables directly to compare a 40 year old woman with a 40 year old man, since the tables were developed with data derived from measurements on men. But every clinician wants to be able to make precisely such comparisons, since he is interested in how two people rate in terms of risk of myocardial infarction whatever may be their age and whether or not both are of the same sex. The problem of transferring the predictive tables to the female sex will be dealt with in extenso in Chapter VIII. The problem of intercomparisons between men of widely separated ages is best handled by bringing in evaluation of absolute risks of coronary heart disease in addition to relative risks.

ABSOLUTE RISK OF CORONARY HEART DISEASE VERSUS RELATIVE RISK

Relative risk estimates for any two individuals describe whether one of them is two, four, ten, or more times as likely to develop clinical coronary heart disease in a particular time interval as is the other. As stated above, such risks have been evaluated for the case where both individuals are of the same, or nearly the same, age. However, if the risk estimates were converted to an *absolute* basis instead of the relative basis, the

year old men with each other. Since for each age decade under consideration a table of risk versus Atherogenic Index and risk versus diastolic blood pressure is needed, such tables must be provided. The table of risk versus diastolic blood pressure, which is based upon the magnitude of the difference in blood pressure for Yater's series of cases of coronary heart disease will be used for all the age groups, since no better data are available for each specific age group. It is doubtful that there would be significant alterations in the relative risk due to blood pressure if separate tables were available for each age group. However, specific data are available from which tables of risk versus Atherogenic Index can be separately constructed for each additional age decade, namely 30-39 years, 50-59 years, and 60-69 years. Tables XV, XVI, and XVII provide these relative risk versus Athero-

TABLE XVII

RELATIVE RISK OF DEVELOPMENT OF MYOCARDIAL INFARCTION FOR VARIOUS ATHEROGENIC INDEX VALUES (60-69 YEAR OLD MEN)

(Corrected for Association of Diastolic Blood Pressure with Atherogenic Index Values)

Atherogenic Index (units)	*Relative Risk of Myocardial Infarction (setting risk = 1.00 at 30 A.I. units)*
30	1.00
35	1.02
40	1.05
45	1.15
50	1.41
55	1.74
60	2.34
65	3.19
70	4.31
75	5.42
80	6.50
85	7.70
90	8.95
95	10.2
100	11.4
105	13.0
110	14.6
115	16.5

fore, for the 35 year man with average Atherogenic Index (70.2 units) and average blood pressure (71.0 mm Hg) as it is for the hypothetical reference man with Atherogenic Index of 30 units and diastolic pressure of 50 mm Hg. Now, since the absolute risk, or incidence rate, of fatal coronary disease is 50 per 100,000 per year for the average man, it must be 50 divided by 8.53, or 5 86 per 100,000 per year for the hypothetical reference man at 30 units of Atherogenic Index and 50 mm Hg. Since all of our relative risk calculations described previously are made in terms of the risk compared with the hypothetical reference man, it becomes immediately possible to convert any relative risk calculated into the absolute risk by simply multiplying by the value 5 86 per 100,000 per year. This may be illustrated as follows: Suppose a 35 year old man has an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg From Table XV, from Atherogenic Index, his risk relative to the hypothetical reference man (A I. = 30 units) is 13.8 times as high. From Table XIV, from diastolic pressure, his risk relative to the reference *man* (BP = 50 mm Hg) is 5 79 times as high. Multiplying these values together, we obtain 13 8x5 79, or 79 9 times as high for the overall relative risk The conversion to absolute risk is achieved by multiplication of 79 9 by 5 86 This yields an absolute risk of 468 per 100,000 per year for the 35 year old man with an Atherogenic Index of 100 units and a blood pressure of 90 mm Hg This value of absolute risk is directly comparable with similarly calculated absolute risks for men *at any age*. *It is*, therefore, evident that having the absolute risk for the hypothetical reference man (A I = 30 units, BP = 50 mm Hg) at each age is highly useful for the purpose of converting relative risks into absolute risks It was demonstrated above how this absolute risk is obtained for the hypothetical reference man of 35 years of age using the combination of the relative risk tables plus the U. S. Vital Statistics to provide the risk for the person with average Atherogenic Index and average blood pressure. Such absolute risks for the hypothetical reference man for each decade have been calculated and are reproduced as follows:

would exist no problem whatever to compare the risk for a 35 year old man with that for a 65 year old man or a man of any age. *Absolute* risks are expressed in terms of the number of men developing clinical coronary heart disease per 100,000 persons exposed in a specific time period, e.g. one year. Thus if a certain *35 year old man belongs to a group where 10 out of 100,000 will develop clinical coronary heart disease in one year and a* certain 65 year old man belongs to a group where 50 out of 100,000 will develop clinical coronary heart disease in one year, it is obviously possible to compare these *absolute* risks *directly* and to state that this 65 year old man has five times the risk of clinical coronary heart disease as the particular 35 year old man under consideration. How are such absolute risks to be obtained for any two men?

The U. S. Vital Statistics provide the average incidence rate of fatal coronary heart disease for men at various ages (see Chapter VII). Let us consider the use of such information to translate relative risks into absolute risks for any particular individual For 35 year old men in the United States the incidence rate of fatal coronary disease is approximately 50 per 100,000 persons *per year. This may be expressed otherwise as the average risk* of fatal coronary heart disease for 35 year old men. To a first approximation (and one completely adequate for all our purposes here) this risk may be considered to be that which applies to the 35 year old man *who has the average values of the Atherogenic Index and of the diastolic blood pressure.*

For this age, average Atherogenic Index=70.2 units, and average diastolic blood pressure=71 0 mm Hg. The question to ask now is "What is the absolute risk for the hypothetical *reference* man of 35 years of age, with an Atherogenic Index of 30 units and a diastolic pressure of 50 mm Hg?" The first step is to compare this hypothetical reference individual with the average man of 35 years of age From Table XV the relative risk of coronary disease for an Atherogenic Index of 70.2 units is 3.79 times that for an Atherogenic Index of 30 units. From Table XIV the relative risk for a diastolic blood pressure of 71 0 mm Hg is 2.25 times that for a diastolic pressure of 50 mm Hg. The *overall* relative risk for 3.79x2.25, or 8 53 times as high, there-

THE QUESTION OF "FALSE POSITIVE" PREDICTIONS

It is worthwhile contemplating the absolute risk values in connection with the question of so-called "false positive" prediction. Thus, for the illustration above for a 65 year old man with a high Atherogenic Index (100 units) and a blood pressure well above average, namely 90 mm Hg, the absolute risk of fatal coronary disease was calculated to be 8217 per 100,000 persons per year Out of 100,000 such men, 8217 would die in one year of coronary heart disease, *but* 91,783 would survive in that year. Evidently many more people would survive the year than would die of coronary disease. There are those who would ask the question, "Does this not mean that the Atherogenic Index-blood pressure risk calculation has falsely indicated a high risk of fatal coronary heart disease?" The answer is unequivocally and emphatically, "No" Even though more persons will survive the year than will die, 8217 deaths per 100,000 is still a very high risk and is in no sense a "false" prediction. The entire point of such risk estimates is the development of an ability to select out of an otherwise homogeneous population sample those persons who carry 2, 5, 10, 20, 100, or 500 times the risk of coronary heart disease death than characterizes other members of the population sample. The issue is *not* selection of some group of *persons*, *all* of whom or *most* of whom will be dead of coronary disease within any specified short time interval. It can readily be shown that the argument concerning "false positives" readily reduces to a logical absurdity Suppose *that a* risk category were identified where 995 out of 1000 persons would be dead of coronary disease in a one year period In this event those who talk of false positives might say that this is good prediction for a one year period, but they could ask about the validity of the risk estimate for the five-minute period just after the blood pressure was determined and the blood sample was withdrawn from Atherogenic Index determination Even for a group of persons in which 995 out of 1000 *will be dead* in one year, it is true that more than 999 out of 1000 would still be alive after five minutes. Does this mean that this group has been *falsely* predicted to show a high risk of coronary disease? Manifestly, this type of reasoning concerning "false positives" *can* lead to ridiculous conclusions and

Age Decade	*Absolute Risk of Fatal Coronary Disease for the Hypothetical Reference Man at Atherogenic Index = 30 Units and Diastolic Pressure = 50 mm Hg.*
30-39 years	3.86 per 100,000 per year
40-49 years	12 9 per 100,000 per year
50-59 years	56 1 per 100,000 per year
60 69 years	124.5 per 100,000 per year

Illustration of how these absolute risks allow direct comparison of men differing widely in age is now in order. In the development above it was shown that a 35 year old man whose Atherogenic Index is 100 units and whose diastolic pressure is 90 mm Hg is 468 per 100,000 per year. How would this compare with the risk of a 65 year old man having the same Atherogenic Index (100 units) and the same diastolic pressure (90 mm Hg)?

For a 65 year old man, from Table XVII, the relative risk for an Atherogenic Index of 100 units is 11.4 times as high as for the reference man with an Atherogenic Index of 30 units. From Table XIV, the relative risk for a diastolic blood pressure of 90 mm Hg is 5.79 times as high as for the reference man with a diastolic pressure of 50 mm Hg. The overall *relative* risk for the 65 year old man with an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg is, therefore, 11.4x5.79, or 66.0 times as high as for the hypothetical reference man of 65 years of age with an Atherogenic Index of 30 units and a diastolic blood pressure of 50 mm Hg. But this hypothetical reference man has an *absolute* risk of fatal coronary heart disease of 124.5 per 100,000 per year Therefore the 65 year old man with an Atherogenic Index of 100 units and a diastolic pressure of 90 mm Hg has an absolute risk of 66 0x124.5, *or 8217 per* 100,000 *per year*. The comparison of this 65 year old man with the 35 year old man having the *same* Atherogenic Index and the same blood pressure is made by dividing 8217 by 468. Therefore the 65 year old man has 17.6 times as high a risk of coronary heart disease as does a 35 year old man, even though both have the same Atherogenic Index and the same blood pressure. The procedure for comparing any two other men at any ages, Atherogenic Indices, and blood pressures would be identical to that just developed.

THE INFLUENCE OF VARIABILITY OF THE ATHEROGENIC INDEX AND BLOOD PRESSURE MEASUREMENTS ON PREDICTIVE POWER

It is of course true that with respect to any biochemical measurement, such as Atherogenic Index value, or any physiological measurement, such as blood pressure, there is a certain degree of fluctuation observed if the measurement is made repeatedly on the same person. This fluctuation in measurement originates from at least two major sources. The first is what may be regarded as *biological* variation, namely, the fact that a human does not show absolutely constant values of very many biochemical or physiologic variables over a period of time. The second major source of variation is that due to technical error of measurement. What we see in the overall when a given variable is measured, such as the Atherogenic Index or the blood pressure, is the combined effect of biological variation and technical error in measurement As a result of the operation of these *two* factors a person will not show exactly the same Atherogenic Index value or blood pressure value determined on two separate occasions either a day, week, month, or year apart. It is true that such variation would tend to move the position of a person somewhat on a scale of risk of future coronary disease This hardly need interfere with the enormous usefulness of the predictive measurement *First* of all, variation of the Atherogenic Index is in general small, although it definitely exists. Hence a person who is in the highest quarter of the population will, in the main, remain in the highest quarter of the population, whereas a person in the lowest quarter of the population with respect to the Atherogenic Index will, in the main, remain in the lowest quarter The precise extent to which Atherogenic Index measurements vary for individuals over a period of one to three years is now known Studies are available for 213 consecutive men between the ages of 20 and 59 years of age upon whom Atherogenic Index measurements were made on one periodic employment examination and on a second examination one to three years later. (Exclusion of the effect of major dietary alterations was achieved by elimination from this series of any men who had gained or lost five or more pounds in weight over the time inter-

away from any constructive approach to the coronary heart disease problem.

It is always pertinent, when confronted with such problems, to review the nature of the objectives toward which one is working. In the prediction of risk of future clinical coronary heart disease, the objective is *utilization* of the information obtained to take constructive steps toward *prevention* of that disease. It would be remarkable indeed if there were a method available to determine that a particular individual is *the* one who will have a myocardial infarction in 30 days If this were possible, every effort could be made to apply preventive measures for this particular individual. Such prediction is simply not possible now nor does it appear that it will be possible in the near future. But the methods described in this chapter do permit identifying individuals with five, ten, or more times the risk of development of clinical coronary heart disease in comparison with average individuals. Can such information be utilized to achieve our objective? Let us suppose that a particular individual has been demonstrated to show *twice* the average risk of development of coronary heart disease during a one year period. Suppose further that such risk can be reduced in half by medical measures If every person whose risk is twice or more than twice average had his or her risk cut in half by medical measures, the net result of such a program would be a lowering of mortality due to coronary heart disease approximately by a factor of two. This would obviously be considered as a major medical triumph. The type of risk estimates developed here allow for progress toward precisely such a goal Great progress can definitely be made in this direction even though it is not possible to predict the date and hour that a specific individual will experience myocardial infarction or even to predict that he *ever* will. While this approach will lead to advice of prophylactic measures for *some* persons who *might* escape the disease even with a high risk, it would be utter folly to underestimate the real potential and power of this type of preventive medical approach to coronary heart disease.

WHO IS IN NEED OF PREDICTION OF THE RISK OF FUTURE MYOCARDIAL INFARCTION?

From the data and calculations presented up to this point it is clear that a population of individuals otherwise comparable can be divided on the basis of lipoprotein and blood pressure measurement into groups characterized by a very low risk of coronary heart disease in a specified time interval, an intermediary risk in the same time interval, or a very high risk in the same time interval. The question facing the clinician is, "What group of individuals is in need of such predictive information concerning the risk of future coronary heart disease?" Certainly those who have already manifested clinical signs and symptoms of overt coronary heart disease are hardly in need of prediction of whether they are prone to develop coronary heart disease. In the population-at-large no one has ever been able to distinguish by standard medical examinations, including electrocardiography, any group of adults who can be said to be free of the risk of future clinical coronary heart disease The suddenness of occurrence of clinical coronary heart disease in "persons in the best of health" eloquently refutes the possibility of pre-selecting by usual means any part of the population which carries an excessive risk from any part of the population which has little or no risk. This being the case it is quite clear that *every adult* in the population represents, without auxiliary special information, a potential candidate for future clinical coronary heart disease. Therefore, every adult in the population is a candidate for *evaluation* of his risk of future coronary heart disease. To be sure, we know from vital statistics for the country that men of 25 years of age have a lesser risk of coronary heart disease than men of 35 years of age, and correspondingly men of 35 years of age have a lesser risk than do men of 45 years of age, etc With respect to imminence of disease, it might be considerably more pertinent to segregate 45 year old men on the basis of risk of future clinical coronary heart disease than to do so for 25 year old men. However another consideration must temper this view. All the evidence indicates that the clinical aspects of coronary heart disease represent a culmination of the slow accumulation of coronary artery narrowing The major predictors of future clinical coronary disease,

val between the two examinations.) The best approximation of the true Atherogenic Index values for these cases is to take the average of the two measurements for each person. When this is done, it is found that the following holds:

(a) 58% of these men varied fewer than 5 Atherogenic Index units from their average value over the 1-3 year period.

(b) 25% of these men varied between 5 and 10 units from their average value over the 1-3 year period.

(c) 13% of these men varied between 10 and 15 units from their average Atherogenic Index value over the 1-3 year period.

(d) Only 4% of these men varied 15 or more units from their average Atherogenic Index value over the 1-3 year period.

Therefore it is relatively rare for a man to be significantly misclassified on the Atherogenic Index—coronary disease risk scale even with a *single* measurement of the Atherogenic Index value. Multiple measurements over a period of time for an individual will allow placement on the risk scale with great precision.

The blood pressure measurement is somewhat more variable both on a biological and technical basis. However, here again if one is interested in assessing the risk of someone with respect to coronary heart disease (and such risk is probably one of the most important measurements that can be made for an individual in health in the effort to safeguard his future health) one can certainly afford to make repeated blood pressure measurements. Since the blood pressure does tend to vary some, one might want to make a series of measurements spaced at specific time intervals to determine the individual's usual, or habitual, blood pressure. Blood pressure measurements taken under relatively standardized conditions should be utilized in coronary disease risk estimates. Thus, if an individual happened to have a single blood pressure value of 100 mm Hg under a single special circumstance, whereas most of the time he is at 80 millimeters of mercury, it would hardly make sense to consider 100 mm Hg as the pressure value to use in assessing coronary disease risk

measure with recent poliomyelitis immunization of adults and, at least for military personnel and travelers, innoculation for several other diseases. However, the idea that vascular disease may enter this realm of preventive medicine is one which will meet with some skepticism and lack of understanding in certain quarters Yet all the evidence points in this direction. There will undoubtedly be those who say the idea of considering every adult as a patient or a potential patient with respect to a disease like coronary heart disease would mean a fabulous task for the medical profession It will be a fabulous task for the medical profession, but one abundantly justified by the fabulous importance of the problem that lies before it in this field. Further, there will be some who will ask whether we might not dispense with individualization in prediction of heart disease risk through identification of those with lipoprotein metabolic errors and/or blood pressure elevation, and instead develop a preventive hygiene that can be advised for the population-at-large broadly without the necessity for individual attention. Preventive hygiene measures on a broad basis are highly desirable where feasible. For example, if it were discovered that a particular atmospheric pollutant resulting from industrialization of our cities were the cause of a particular disease, certainly the best measure for minimization of the hazard due to this pollutant would be a concerted attempt to rid the atmosphere of it This would represent broad-scale application of a generalized hygiene Similarly, if it could be shown that a specific dietary element were injurious to a large number of individuals or to all, one could recommend a generalized hygiene to eliminate this particular noxious agent from the dietary environment There is every reason to make progress in this direction of generalizing our efforts toward a preventive hygiene for coronary heart disease. However, as the evidence develops in this area, it appears more and more that *individualization* will be needed, and needed *over and above any such generalized measures* Thus, it is now known that in certain individuals the S_f0-20 lipoprotein elevation is the primary reason for an increased risk of future clinical coronary heart disease. In other individuals the S_f20-400 lipoprotein elevation is the primary reason for an increased risk of future coronary heart dis-

namely the lipoprotein levels and the blood pressure, appear to derive their relationship with clinical coronary heart disease via their relationship with coronary arteriosclerotic narrowing. Therefore, if a preventive regimen is to be devised for persons with high risks, the prediction of risk should be accomplished as early as feasible, in order to inhibit the slowly developing coronary artery narrowing, and the corresponding accumulation of risk of ultimate clinical coronary heart disease. This means that the earlier it is possible to use predictive information, the more favorable the outlook for accomplishments in minimization of the risk of ultimate development of overt coronary heart disease. By the time a man is in his twenties his lipoprotein levels can certainly provide a great deal of information concerning the risk of later clinical coronary heart disease. This is the appropriate time to start evaluation of risk. Further, since there is no way of excluding *anyone* in the population as a potential bearer of a high risk of future coronary heart disease, the need for screening the future risk of coronary heart disease extends over the entire population of adults of any country This is undoubtedly a rather radical concept to some. However, some reflection on the problem will readily reveal that unless and until this concept is understood and utilized broadly by the medical profession, the real hope of inhibiting coronary heart disease and cutting down its enormous morbidity and mortality can hardly be realized. This means an entirely new concept for the physician interested in vascular disease as to who is a "patient." We have, in adult medicine, for so long been oriented toward the therapeutic side of medicine, treating diseases once they have become clinically manifest, that it will undoubtedly be difficult, both from the point of view of the physician and of the potential patient, to alter this concept Yet the concept of preventive medicine has taken hold and is taking hold in new areas every day In pediatric practice, for example, the idea of minimizing the risk of such entities as pertussis, typhoid fever, tetanus, diphtheria, poliomyelitis, and other diseases is well established, and immunization of most children is routine. Every child is regarded as a potential candidate for these diseases and hence is deserving of preventive medicine. In the adult field this has been extended to some

many industries have for several years been in the habit of having annual preventive medical check-ups. Such preventive medical check-ups are gradually coming to include additional features of examination, laboratory and clinical, which may discover predisposition to certain diseases at a time when preventive efforts may be really effective. This concept of preventive hygiene is not new, but simply one that requires extremely broad expansion to include thousands of times the numbers of individuals who are now covered by it But progress of this sort, considering the educational aspects involved, may take many years to achieve. It would be naive to believe that simply stating the problem to the physician population and through that group to the public-at-large would see overnight the accomplishment of the desired end It is very important to attempt to lower the time gap between *application* of what we have available to us in our armamentarium of prevention of disease and its actual use to as few years as possible During such an interim time period a great deal can be accomplished by broadening the use of predictive methods for determining the risk of coronary disease to include at least those people who carry the most excessive risk of early coronary heart disease.

As an illustration of this approach, some glaring examples of such groups with very high potential coronary disease risk deserve consideration There exist perhaps as many as one percent of the individuals in the population of the United States who come from families characterized by a marked heritable tendency to have abnormally high levels of lipoproteins of one class or another. In such families overt xanthomata are common, xanthoma tuberosum, xanthoma planum of the hands, xanthoma tendinosum, or xanthelasmata about the eyelids. In these families not all individuals are afflicted with the abnormally high lipoprotein levels but many are. Unless the members of such families are already characterized by manifest xanthomatosis, they go unrecognized and nothing is done for them Some with overt xanthomatosis who have not yet developed overt cardiovascular disease are discovered by physicians because the patients are concerned over the cosmetic aspects of their lesions

ease. In this latter group, the S_f0-20 lipoproteins may be moderate or even very low in level. In still other individuals it is an elevation of all the lipoprotein classes in this general region from S_f0-400 that accounts for the risk of future coronary heart disease. And added to each of these possibilities, there is the factor of elevation of blood pressure together with one or another type of lipoprotein elevation that creates a high risk of future coronary heart disease. *The metabolic factors which control the level of the* S_f0-20 lipoproteins are not in general the same as those that control the level of the S_f20-400 lipoproteins. This is already evident from the fact that individuals can be high in one class of lipoproteins but low in another. It appears highly unlikely that the future will readily see a dietary approach or a pharmaceutical approach that will at once correct *all* the different types of metabolic aberrations that lead to lipoprotein elevation. Therefore individualized attention appears inevitable Indeed a regimen that might favorably affect one lipoprotein class can be very unfavorable for another class. Were sights focussed on the correction of just one of the lipoprotein classes involved without proper attention to the others in a mass generalization of a dietary or pharmacologic preventive hygiene, a great deal of harm might accrue to certain individuals. Such a result could hardly be called an aim of preventive medicine or of medicine in general. Thus, the existence of several types of defects that can lead to an increased risk of clinical coronary heart disease and the unlikely prospect that any simple specific preventive measure will work for everyone on a "blind" basis means that individualization of preventive medical efforts appears essential. The facilities for measurement of the status of every adult individual with respect to lipoprotein level on a schedule such as every one to three years beyond the age of 25 years have long been available. The problem will, first, be largely one of having the physician population recognize the need for such a preventive approach to the problem of coronary heart disease. The public will then need to be educated by the physician concerning the vital role of *preventive* medicine with respect to coronary heart disease Already, many individuals under the advice of their own competent physicians and the executives of

excessive rates. Such persons are, therefore, in need of preventive measures to avert the same type of clinical occurrence as that experienced by the index case. Certainly for anyone with overt coronary heart disease below the age of 40 years, a lipoprotein analysis in all blood relatives is urgent. With less force the same would hold true for the families of persons developing overt coronary heart disease between 40 and 50 years of age. Another stigma that is common in the population and which is at times associated with a lipoprotein disorder on a heredofamilial basis is arcus senilis. The presence of a well-marked arcus senilis in a relatively young person, for example, under 40 years of age, distinctly suggests the individual deserves an early lipoprotein analysis. A surprisingly high frequency of elevation of the S_f0-12 or S_f0-20 lipoproteins will be found in such cases.

Diabetes mellitus will be considered in extenso in Chapter XII However at this time it can be emphasized that what excessive risk of coronary heart disease does exist for persons with diabetes mellitus arises largely, if not completely, from elevation of lipoprotein levels or elevation of blood pressure, or both. The lipoprotein and blood pressure status of every diabetic patient deserves early determination, both from the prognostic and management aspects of that person's disease There is no longer any reason for the blanket generalization to the diabetic patient that he carries a hazard of premature coronary heart disease simply because he is diabetic. Such risk can now be determined precisely If the particular diabetic patient should be one of the many fortunate diabetics who do not show the elevation in lipoproteins or the elevation in blood pressure which would accompany an excessive risk of coronary heart disease, he could be vigorously re-assured concerning his outlook by his medical advisor Thus, even though there may be a period of time before the population-at-large is evaluated with respect to lipoprotein and blood pressure status, every diabetic deserves an early evaluation Still another group that deserves consideration comprises those individuals who at one time or another have been treated for thyroid disease A large majority of these may have been treated for a previous hyperthyroidism and some, for goiter without hyperthyroidism. Many of these individuals are

tion is the major feature of therapy. Yet it is well-known that the individuals in such families who are characterized by extremely high lipoprotein levels are prime candidates for very early coronary heart disease and for other related entities such as peripheral vascular disease and cerebral vascular disease. The rate at which the ranks of such families are decreased by premature deaths from coronary heart disease and its related entities is truly appalling, with a large proportion of deaths occurring below forty years of age. For those persons who manifest xanthomatosis there is not a great deal of difficulty in clinical diagnosis of the existence of the xanthomatosis, but all too often nothing is clinically done for the members of these families without the overt lesions For example, in a family where any individual has xanthoma tendinosum with its attendant massive S_f0-12 or S_f0-20 lipoprotein elevation, there exists the high likelihood that brothers, sisters, other relatives, and offspring, even below the age of 5 years, may already have the same massive lipoprotein defect as the index case. These individuals, not yet having developed skin lesions or tendon lesions, are unaware of the tremendous hazard of coronary heart disease they may have inherited and nothing is generally done to attempt to reduce this hazard In such families *every* blood relative of individuals known to be characterized by xanthomatosis of any form requires urgent evaluation of the lipoprotein status as a first step toward broader application of the principle of preventive medicine in coronary heart disease.

Other familial situations would deserve early consideration of an evaluation of the lipoprotein and blood pressure status for members of the family It is the rule to find that young individuals who develop clinical coronary heart disease show *extremely* elevated lipoprotein levels, with this elevation frequently being heredo-familial in origin Siblings of such individuals, parents and children may well be found to be afflicted with a similar lipoprotein disorder. Hence, when coronary disease occurs at an early age in a person, it is very pertinent to examine the lipoprotein status of every blood relative who is available in the effort to discover other members of the family in whom the coronary heart disease risk may be building up at

Chapter VI

THE FAMILIAL ASPECTS OF CORONARY HEART DISEASE

One of the most widespread impressions in medicine concerning coronary heart disease is that it occurs prematurely in certain families. Some cardiologists have crystallized this impression with statements to the effect that perhaps one of the best ways to avoid clinical coronary heart disease is to choose one's ancestors wisely The widespread character of this concept implies that there must be some evidence to support it, and indeed there does exist a certain amount of evidence. However, it can be stated at the outset that the relationship between familial factors and coronary heart disease is far from a perfect one. Therefore, any broad *generalization* based upon a statement that a family history of longevity can be relied upon to protect against coronary heart disease, or that a very poor family history insures that coronary disease will occur in a given individual will be very far from the truth

The real question of interest is whether or not familial factors operate in coronary heart disease in the population-at-large, out of which is drawn the vast bulk of our patients with early clinical coronary heart disease In certain special types of families the hereditary, or heredo-familial, aspect of clinical coronary heart disease is unquestioned, since a very solid body of evidence has implicated a familial factor in these special groups predisposing to the occurrence of coronary disease. This is true of those families in which a hyperlipoproteinemia of some variety is present Earlier, such families had been described in terms of elevation of the serum cholesterol level or the blood total lipid level, but now such entities can be more precisely defined and delineated in terms of the particular spectrum of lipoproteins

followed for a short period of time in the medical center or in the office in which they were originally diagnosed and treated. Thyroid replacement therapy has been provided for many such patients who were left with a mild residual hypothroidism. Yet it is very common for the individual himself to assume that such replacement therapy is temporary and eventually he may stop taking thyroid substance and may remain for years in a hypothyroid state. Such individuals may not feel seriously ill or have sufficient special complaints referable to their thyroid status to seek medical care. If they have been affected by thyroid deficiency to the extent that they acquire the marked elevation of S_f0-20 lipoproteins which characterizes thyroid deficiency (see Chapter XIII), they may be carrying a markedly excessive risk of future clinical coronary heart disease. Therefore, any individual who has, for whatever reason, at one time had a thyroidectomy or a treatment of thyroid disease by destructive agents such as x-ray or radioactive iodine certainly deserves a periodic evaluation of the lipoprotein status to determine whether there is any need for replacement therapy with thyroid substance or one of its congeners.

As one considers the several possibilities, familial lipoprotein derangements, thyroid disorders, diabetes mellitus, families of individuals with early coronary disease, and others, it becomes apparent that the groups in need of early evaluation of their status with respect to risk of coronary disease constitute large numbers of persons. These groups certainly represent the basis for a minimum effort that the medical profession should make in a start toward a significant preventive medicine with respect to coronary heart disease Ultimately this effort must extend to everyone in the population-at-large

elevation. Xanthoma tuberosum is common in these families. Coronary heart disease at an early age is also rampant in this particular heredo familial disorder. Again, there appears to exist no evidence that, at the same degree of elevation of lipoprotein level, there would be any difference in the prognosis with respect to early coronary heart disease in the presence or absence of xanthomatosis. A third group of individuals showing a heredo-familial disorder of lipoprotein levels is that known as the "essential hyperlipemia" group This group of individuals is characterized in general by the absence of xanthomatous lesions These families are discovered when a member of the family is incidentally found to show markedly creamy serum in the fasting state They are characterized by massive elevation in lipoproteins from s_f20 to s_f100, and in most cases, additional massive elevation of lipoprotein levels of those from s_f100 all the way to chylomicrons It is the presence of the very large lipoproteins in high concentration that accounts wholly for the extreme turbidity of the serum in such cases. Characteristically, the s_f0-12 lipoprotein levels are low in such cases, and the s_f12-20 lipoprotein levels are usually not different from those in the population-at-large For some reason there is an erroneous concept in the literature that such individuals seem to be free of the risk of coronary heart disease. This concept is distinctly incorrect, for when such persons have the elevation of s_f20-400 lipoproteins, they carry the high risk of coronary heart disease associated with such an elevation. Most likely the reason for the good prognosis previously assigned to these individuals is that the handful of cases reported in the literature have in the main been children and very young adults. As a result these individuals have been thought to be free of coronary disease risk in spite of their lipoprotein elevation, when actually the reason why they are free of coronary heart disease is that they have been studied at such a relatively early age

Even if all these various heredo-familial lipoprotein disorders are combined, they may still be regarded as a rather special group when compared with the population-at-large. Indeed such groups are considered so special that some workers refer to their disease of the vascular system as xanthomatosis of the vascular

which is abnormal[32]. Families do exist with extreme elevation of one or another lipoprotein class, and in these families it is well documented by evidence reported throughout the world that premature clinical coronary heart disease is rampant. To be sure, *some* of the members of these families escape premature clinical coronary heart disease, but that there is a marked increase in the frequency of such disease in these families cannot be doubted. One such type of family is that characterized by massive elevation of the s_f0-12 or s_f0-20 lipoprotein class. In members of these families where the lipoprotein elevation is extreme and where enough time has elapsed, xanthomatosis in the form of xanthelasma (xanthoma of the eyelids), xanthoma tendinosum, and even planar xanthomatosis of the palms is observed There has been some debate in the literature concerning whether or not those members of the family who show the elevation in the blood lipids without the overt xanthomatosis really carry any pre-disposition to coronary heart disease[33]. There is very little question but that the real essence of this problem is that, in order to develop xanthomatosis, the level of lipoproteins has to be quite high and this lipoprotein elevation has to have existed for some period of time. The absence of xanthomatosis in the presence of a high lipoprotein level is quite often traceable to the fact that the individual is relatively young[34]. Given enough time, many of these individuals do develop the xanthomatosis. There exists no reason to expect that the lipoprotein elevation without xanthomatosis carries any different prognosis with respect to early coronary heart disease than does the same degree of lipoprotein elevation with the xanthomatosis, provided of course that any age differential that exists is taken into account. A second type of disorder which is a familial one is that characterized by massive elevation primarily in the S_f12-400 class of lipoproteins, especially the S_f20-400 part of this class of lipoproteins. In such families the lipoprotein derangement is also an inheritable trait with those members of the family who do inherit it showing the same lipoprotein disorder, namely, elevation of the s_f12-400 or s_f20-400 lipoprotein class. It is interesting that, on the average, such individuals show a depression of the s_f0-12 lipoprotein level rather than an

directions. The specific evidence available from such studies deserves critical examination here

DIRECT STUDIES OF THE INCIDENCE OF CARDIOVASCULAR DISEASE IN THE FAMILIES OF INDIVIDUALS WITH OVERT CORONARY HEART DISEASE

One study of the familial patterns in patients with coronary heart disease is that of Gertler and White[34], a part of their overall study of ninety-seven men who had developed clinical coronary heart disease below the age of 40 years. In that study there were 97 men who had developed coronary heart disease below the age of 40 years and 97 matched controls, matched as well as possible by age, sex, and by other variables such as occupation The matched group of controls was overtly healthy and free of any symptoms or signs of clinical coronary heart disease. Interviews conducted in the course of the examination of all these subjects developed data concerning the incidence of cardiovascular disease and deaths due to cardiovascular disease in the mothers, in the fathers, and in the siblings of the 97 men with clinical coronary heart disease and in the relatives of the group of matched controls It was found by Gertler and White that a significantly higher percentage of the fathers of men with coronary heart disease below 40 years had had cardiovascular disease or had died of cardiovascular disease than of the fathers of the matched control group The trend was in the same direction for the mothers of the men with coronary disease below the age of 40 years as compared with the mothers of the men in the matched control group, although the total number of cases of cardiovascular disease among the mothers was too small to be statistically significant Similarly, it was found that the brothers of the men with coronary heart disease below 40 years showed a higher reported incidence of cardiovascular disease than did brothers of the men in the matched control group The general conclusion that would be drawn from the study of the Gertler and White material is that cardiovascular disease is significantly more frequent in the families of men who suffer coronary disease below the age of 40 years than in men of the same age group free of overt coronary heart disease Unfortunately, one major failing

system rather than arteriosclerosis of the vascular system. There does not exist a valid justification for differentiation of the vascular lesions in the individuals in xanthomatotic families with massive lipoprotein elevation from the arteriosclerosis which occurs in the population-at-large. These special individuals are developing such vascular disease very rapidly, associated with their extremely high levels of the various lipoprotein classes, but inasmuch as their lipoproteins appear to be of the same chemical types as those that occur in individuals of the population-at-large[35], the disease in their arteries hardly deserves the special termination, xanthomatosis of the arteries. What every physician would like to know is the extent to which familial factors may operate in coronary heart disease *in the population-at-large* rather than in coronary heart disease in these special families. A sound evaluation of this issue requires careful studies of one or more types. A careful study could be undertaken to determine the incidence rate of coronary heart disease in siblings of persons in the population-at-large who have demonstrated premature clinical coronary disease instead of the incidence in siblings of selected persons from known xanthomatotic or hyperlipoproteinemic famlies. A similar study could be undertaken to determine the history of coronary heart disease in the parents of a representative sample of persons with clinical coronary heart disease selected out of the population-at-large. Thirdly, the problem can be approached in a different manner by a correlation study of the family history of various individuals in a large population sample with those factors known to be associated with coronary heart disease. Since the level of certain lipoproteins and the blood pressure are such factors, it is important to measure the extent to which either is related, if at all, with the family history of coronary heart disease. As a variant of this study measurements of the lipoproteins in the families of a large number of individuals chosen at random out of the population-at-large can be made to determine whether or not there exists a correlation in lipoprotein levels for family members in general such as is known to exist in markedly hyperlipoproteinemic and xanthomatotic families. Some real progress has been made in several of these

may have biassed the outcome of the family history surveys. To be sure, the size of the difference in familial incidence of cardiovascular disease between Yater's myocardial infarction survivors and his traumatic injury control group is so large that a considerable bias could be tolerated with appreciably altering his conclusions concerning family history of cardiovascular disease. Both studies should be regarded as providing highly suggestive evidence, evidence that should be supplemented by approaches free of the potential bias inherent in retrospective questioning.

A totally different avenue of approach is to determine certain bio-chemical or physiological variables in a representative sample of the population-at-large and, *independently*, to determine the family history of longevity and cardiovascular disease for the same persons. If the biochemical or physiological variables are themselves known to be factors in coronary heart disease, any correlations observed would be of extreme interest. Such a study is free of the objections inherent in that of the retrospective questioning of individuals with coronary disease, since the determination of the biochemical variable, such as the lipoprotein level, and of the physiological variable, such as the blood pressure, is wholly independent of the questioning of the individuals. Furthermore, since the individuals do not know either their blood pressure value or their lipoprotein findings, there is no chance for biassing in a direction either for or against a history of familial cardiovascular disease with unfavorable values of the particular variables under consideration. We may be sure that in such a study *some* positive association of elevation of lipoprotein level with familial cardiovascular disease will necessarily be discovered. This is so because of the existence of the well-known special families previously described with either the s_f0-20 lipoprotein elevation or with the s_f20-400 lipoprotein elevation. Inasmuch as such categories of individuals are known to have a high incidence of cardiovascular disease in their families, any such cases in the population sample make for the positive association. The question at hand is to what extent such families are represented in a cross-sectional survey of the population-at-large. It is certain that many such families have not been recognized and will be discovered in any cross-section of the

characterizes studies of this type, a failing which was carefully alluded to by Gertler and White and in their publication, namely that this is in essence a *retrospective study* involving the questioning of a group of individuals who have coronary disease themselves and a group without such disease. Inasmuch as it is common for patients with a particular disease to be seeking possible explanations for their own disease, it would not be surprising if the men who had clinical coronary heart disease below the age of 40 years might be more likely to remember the occurrence of such disease in members of their family. Alternatively, if the diagnosis had been in doubt for members of their families, they might well be inclined to have remembered better the possibility that such a diagnosis was one of cardiovascular disease. Any such effects operating for the patients with clinical coronary heart disease would tend to make coronary or cardiovascular disease appear more frequent in their relatives, thus having the effect of biassing the result in the direction of the outcome that was observed.

Yater and co-workers[24], in their classic studies of 866 cases of men with coronary heart disease between the ages of 18 and 39 years, made observations analogous to those of Gertler and White. They questioned 392 men who had survived a well-documented, typical attack of myocardial infarction while in the Army and they questioned a control group of 210 men (amputees or those hospitalized for gunshot wounds) concerning family history of heart disease Hypertension and/or coronary artery disease was reported for the immediate family of 41% of the myocardial infarction cases, whereas these entities were reported in only 13% of the traumatic injury control group of men In the "immediate" family Yater includes father, mother, brothers, and sisters. The conclusion is the same as that arrived at by Gertler and White, but unfortunately the defect in the study is identical with that in the study of Gertler and White, namely the possible biassing of results due to awareness of coronary heart disease as a problem amongst the myocardial infarction survivors.

Unfortunately in both the studies of Gertler and White and those of Yater and co-workers, it is virtually impossible to determine the extent to which the retrospective features of the studies

exclude such listed causes as accidental death or suicide. However, it is entirely possible that a sudden coronary occlusion could have led to a fatal accident and that illness such as coronary heart disease could have been a factor contributing to suicide. Therefore it seems most reasonable to test for differences in lipoprotein levels, Atherogenic Index values, and blood pressures between the group of men reporting one or both parents dead as of the examination time and the group of men both of whose parents were alive at that time without any exclusion. In additional special consideration was given to the group reporting death due to heart disease in either the mother or father. Since often the person is unable to state what type of heart disease was the cause of death in the parent, the overall category "heart disease" was utilized. Any effects observed that are provably significant will, no doubt, be *underestimated,* for heart disease other than coronary heart disease would not be anticipated to be associated with lipoprotein levels[38]. For example, rheumatic heart disease shows no association with lipoproteins. Thus this entire approach is a conservative one aimed at discovering at least any *minimum* familial aspects of coronary heart disease.

THE LIPOPROTEIN AND ATHEROGENIC INDEX VALUES IN RELATION TO FAMILY HISTORY

Of the 878 men between 30 and 39 years under study, 421 men reported that *either the father, the mother,* or both were dead at the time of examination whereas 457 men reported that both parents were alive at the time of examination. The mean value for all lipoprotein classes, for the Atherogenic Index, for the diastolic blood pressure, and for the ages of the men in both groups are presented in Table XVIII. It is noted that the average age of those men reporting one or both parents dead is 34.5 years, whereas the average age for those men reporting both parents alive is 33.7 years. Therefore it is appropriate to make the small correction in all values for the latter group for the 0.8 year difference in average age. When this is done, the values for each class of lipoproteins and the Atherogenic Index values,

population-at-large. The extent to which such cases will be diluted out by the very much larger group of cases not characterized by extreme derangement of lipoprotein levels or to which such cases will be supplemented by cases with a mild lipoprotein derangement, familial in origin, cannot be predicted in advance. However, a *mild* derangement in a biochemical variable or physiologic variable associated with familial cardiovascular disease should manifest itself by a shift in all parts of the distribution of cases on the particular variable to higher values for the group with a positive family history of cardiovascular disease. If the only derangement that exists is that in families with the massive defect, this would manifest itself instead as just a small number of cases in a tail of the distribution curve.

An investigation of precisely this type has now been completed[37], including lipoprotein measurement, blood pressure measurement, and a family history evaluation for 878 employed men between the ages of 30 and 39 years. Blood was taken for lipoprotein analysis and blood pressure measurements were made in the course of routine periodic medical employment examinations, the individual being completely unaware that any such research studies were involved. In a separate part of the same examination all individuals were asked to fill out a routine questionnaire concerning the presence or absence of heart disease or other diseases in their families and the cause of death if their parents were dead. Numerous possible subdivisions of family history are of interest in this type of study. While it would be ideal to have available documented histories concerning coronary heart disease in the parents of the population sample under study, this ideal is very difficult to achieve in practise. Most individuals have only a general idea of cause of death in their parents, especially if such death had occurred several years ago. One major criterion that is reliable is the determination of whether or not the parents are dead or alive for all the subjects under study. Beyond this the information obtained becomes progressively more vague. Such statements as "dead of natural causes" can mean just about anything, but many individuals know no more than this as a cause of death in their parents. In the group of deaths, it might at first thought seem reasonable to

the difference in values, and the significance test upon this difference are as listed below.

	One or Both Parents Dead	Both Parents Alive (Corrected for Age)	Difference	Significance Test
S_f0-12 lipoproteins	360.5	351.0	9.5	Not significant
S_f12-20 lipoproteins	53.0	50.8	2.2	Not significant
S_f20-100 lipoproteins	97.0	90.5	6.5	$p = 0.1$
S_f100-400 lipoproteins	57.9	48.2	9.7	$p = 0.02$
Atherogenic Index	72.4	68.1	4.3	$p < 0.01$

The Atherogenic Index, which expresses the composite important information, is clearly higher for the group with one or both parents dead than for the group with both parents alive, even after correction for the slight age difference between the groups (less than one chance in 100 that random sampling would give rise to this large a difference). Therefore a family history of longevity is definitely associated with lower average Atherogenic Index values in the offspring. One possible objection must be considered. This is the possibility that the group with deaths in the parents may on the average be represented by parents who had their children at a later period in life. But this cannot be of any consequence since by separate test it has been shown that the lipoprotein values and Atherogenic Index values in offspring are the same independent of whether *either* or both parents are in their twenties, thirties, or forties at the time of birth of their offspring. Therefore, the only conclusion is that a family *history* of early death in *one* or both parents is associated with higher average Atherogenic Index values in the offspring.

The next question worthy of consideration is whether the observed, significant effect occurs because of a few individuals with very high lipoprotein-atherogenic index values or because of a *general* shift toward higher values in the offspring of parents who die at a relatively early age. One good test of this is a determination of the fraction of parents dead for offspring in each Atherogenic Index category. If the fraction of dead rises smoothly with increase in A.I. values *even* in the moderate A.I. value ranges, it can be inferred that a general shift exists rather than that all the effect is due to the presence of a small number

TABLE XVIII

THE RELATIONSHIP OF PARENTAL LONGEVITY WITH LIPOPROTEIN LEVELS, ATHEROGENIC INDEX VALUES AND DIASTOLIC BLOOD PRESSURES IN OVERTLY HEALTHY 30-39 YEAR OLD MEN

GROUP	*Number of Cases*	*Mean Age (years)*	*Mean S_f0-12 (mg/100ml)*	*Mean S_f12-20 (mg/100ml)*	*Mean S_f20-100 (mg/100ml)*	*Mean S_f100-400 (mg/100ml)*	*Mean A.I. Value (units)*	*Mean Diastolic Blood Pressure mm Hg*
Men Reporting Both Parents Alive	457	33.7	348.6	50.0	88.9	47.0	67.3	69.2
Men Reporting One or Both Parents Dead (Death of all causes)	421	34.5	360.5	53.0	97.0	57.9	72.4	70.6

TABLE XX

THE RELATIONSHIP OF A HISTORY OF FATHER'S DEATH OF HEART DISEASE WITH LIPOPROTEIN LEVELS, ATHEROGENIC INDEX VALUES, AND DIASTOLIC BLOOD PRESSURE IN OVERTLY HEALTHY 30-39 YEAR OLD MEN

GROUP	Mean Age (years)	Mean S_f0-12 (mg/100ml)	Mean S_f12-20 (mg/100ml)	Mean S_f20-100 (mg/100ml)	Mean S_f100-400 (mg/100ml)	Atherogenic Index (units)	Diastolic Blood Pressure (mm Hg)
All 878 Men Studied	34.1	354.3	51.5	92.7	52.2	69.7	69.9
122 Men Reporting Father was Dead of Heart Disease	34.6	366.6	54.2	110.0	75.0	78.5	72.5

of individuals with very high Atherogenic Index values. Such data are presented in Table XIX. It is evident that at least above 70 A.I. units the fraction dead is rising smoothly with increasing A.I. values, indicating that short-lived parents are associated with a *general shift* toward higher A.I. values in offsprings, rather than with the presence of a relatively small proportion of off-springs with extremely high A.I. values. The relationship of A.I. value in offspring to longevity in parents is by no means small, since comparison of the group with A.I. values above 110 units with the group having A.I. values below 60 units shows a 52% increase in the fraction with one or both parents dead (0.64 compared with 0.42).

Of the 421 men in the 30-39 year age group studied, 122 men reported the father to be dead of heart disease. A highly rigorous test of the association of death of a father due to heart disease with elevation of lipoprotein level of Atherogenic Index value is to determine whether the 122 men with fathers dead of heart disease show significantly different levels from all other persons in the group (878-122, or 756). The data necessary for this comparison are presented in Table XX. The men with

TABLE XIX

RELATIVE PROBABILITY OF HAVING ONE OR BOTH PARENTS DEAD IN RELATION TO ATHEROGENIC INDEX VALUES IN 30-39 YEAR OLD MALE OFFSPRING

Atherogenic Index Range (units)	*Fraction of Subjects Having One or Both Parents Dead*	*Relative Probability of Having One or Both Parents Dead (setting value = 1.00 for A.I. values below 40 units)*
< 40	23 out of 55, or 0 42	1 00
40-49	50 out of 120, or 0.42	1 00
50-59	71 out of 162, or 0 44	1 05
60 69	65 out of 154, or 0 42	1 00
70-79	71 out of 145, or 0.49	1 17
80-89	52 out of 94, or 0 55	1.31
90 99	31 out of 59, or 0.53	1 26
100 or higher	46 out of 80, or 0 58	1 38
110 or higher	36 out of 56, or 0 64	1.52
130 or higher	21 out of 28, or 0.75	1 79

For men of 35 years of age with A.I. values over 110 units there is approximately a five-fold greater fraction of fathers already dead of heart disease in comparison with the fraction of fathers dead of heart disease for 35 year old men with A.I. values below 50 units.

A similar test was carried out to determine any possible association of death of the mother of heart disease with lipoprotein and Atherogenic Index values in the offspring. Unfortunately for this test, but expectedly, the number of men out of the total of 878 with mothers dead of heart disease was only 31 cases While the Atherogenic Index was higher (75 0 units) for the men whose mothers were dead of heart disease than for the overall group of 878 men (69.7 units), the number of cases available did not allow for proof that this difference in A I. values was significant However, the class of lipoproteins which had shown the most striking elevation in level for men with fathers dead of heart disease, the S_f100-400 lipoproteins, *could* also be proven significantly higher for the men whose mothers were dead of heart disease than for the men in the overall group, ($p = 0\,02$)

TABLE XXI

RELATIVE PROBABILITY OF HAVING FATHER DEAD OF HEART DISEASE IN RELATION TO ATHEROGENIC INDEX VALUES IN 30 39 YEAR OLD MALE OFFSPRING

Atherogenic Index Range (units)	*Fraction of Subjects Having Father Dead of Heart Disease*	*Relative Probability of Having Father Dead of Heart Disease (setting value = 1.00 for A I values below 40 units)*
< 40	3 out of 56, or 0 054	1 00
40-49	14 out of 121, or 0 116	2 15
50-59	17 out of 165, or 0 103	1 91
60 69	18 out of 156 or 0 115	2 13
70 79	26 out of 147, or 0 179	3.28
80 89	9 out of 95, or 0 095	1.76
90 99	14 out of 60, or 0.233	4.32
100 or higher	21 out of 80, or 0.263	4 87
110 or higher	16 out of 55, or 0.291	5.39
130 or higher	11 out of 28, or 0.393	7.28

fathers dead of heart disease were on the average 0.5 years older than the overall group of 878 men (34.6 years versus 34 I years). The various lipoprotein values and the Atherogenic Index values are readily corrected for this 0.5 year age difference. The age-corrected values and the difference between the overall group of men and that part of the group with fathers dead of heart disease, together *with significance tests of such differences are listed* below:

	Overall Group	*Father Dead of Heart Disease*	*Difference*	*Significance Test*
		(Corrected for 0.5 Year Age Difference)		
s_f0-12 lipoproteins =	354.3	365.1	10.8	Not significant
s_f12-20 lipoproteins =	*51.5*	*53.7*	*2.2*	*Not significant*
s_f20-100 lipoproteins =	92.7	109.0	16.3	$p < 0.001$
s_f100-400 lipoproteins =	52.2	71.2	22.0	$p < 0.001$
Atherogenic Index =	69.7	78.0	8.3	$p < 0.001$

These data leave little question but that the group of men whose fathers are already dead of heart disease are quite different in lipoprotein and Atherogenic Index values, from the overall *group of men of the same age* (*For the Atherogenic Index,* the chance that random sampling could have given rise to the observed difference is less than one in 1000). Here again it is of interest to know whether the effect is accounted for by a relatively small proportion of men with extremely high Atherogenic Index values or whether it is a continuous effect operating over the entire range of Atherogenic Index values encountered In Table XXI are presented the data concerning the fraction of men in the overall group whose fathers are dead of heart disease ranked by Atherogenic Index value of the offspring. Inspection of those data indicates clearly that the effect is a smoothly *continuous one over essentially the entire* Atherogenic Index range, with a rising fraction dead of heart disease with rising Atherogenic Index value. Thus the effect is not accounted for only by a small group of men with very high Atherogenic Index values. The comparison of the death rate due *to heart* disease in fathers of men with high Atherogenic Index values with that for men with very low Atherogenic Index values is startling.

nary heart disease and a family history of heart disease. Furthermore, such evidence is free of any of the possibilities of retrospective bias that may characterize questioning men with coronary heart disease concerning the presence or absence of heart disease in their families. In this study of lipoproteins, Atherogenic Index and blood pressure levels versus family history, there is no knowledge available to the experimental subject concerning these measurements that might have conceivably biassed his reply to the questionnaire concerning family history. It is of interest that these studies, free of the possibility of retrospective bias, do lead to precisely the same type of conclusion arrived at by Yater and co-workers and independently by Gertler and White through their retrospective studies of the family history in young men with coronary heart disease

POSSIBLE MECHANISM OF MEDIATION OF EFFECT OF FAMILY HISTORY UPON ATHEROGENIC INDEX VALUES

Establishment that the 30-39 year old offspring of fathers who die prematurely of heart disease show higher Atherogenic Index values than do members of the overall 30-39 year population sample leads immediately to the question of how such an effect is mediated A familial relationship can be on a hereditary, or genetic, basis or it can be the result of environmental features common to the members of a particular family It is sometimes a matter of no little difficulty to distinguish these two mechanisms Further, the situation may even be complicated by the inheritance of a trait that alters the offspring's response to a particular environmental influence.

In subsequent chapters two features of humans associated with lipoprotein-Atherogenic Index alteration will be discussed in detail These are the degree of overweight and the cigarette smoking habit. There are elements in both these features that suggest familial factors may be of consequence Overweight may conceivably be associated with hereditary tendencies to hypometabolism, or to overeating, or with familial patterns of overeating Cigarette smoking may conceivably be a reflection, in part at least, of a type of temperament that could be heritable or even

THE BLOOD PRESSURE IN RELATION TO FAMILY HISTORY

All the considerations above apply to one major factor involved in the development of coronary heart disease, namely the lipoprotein-Atherogenic Index value The diastolic blood pressure level is, from previous discussion (See Chapter IV), the other major factor involved in determination of coronary heart disease risk. Hence any possible relationship of blood pressure in offspring with family history of early death or of heart disease specifically is of importance. In Table XVIII are presented the data for the diastolic blood pressures in the 421 men with one or both parents dead and for the 457 men with both parents living It is not possible to show, from these data that the diastolic blood pressure is significantly different for those men with parental history of early death as compared with a parental history of longevity. The second pertinent comparison is that for the 122 with fathers dead of heart disease with the overall group of 878 men. This comparison is tabulated below.

	Mean Age (Years)	*Mean Diastolic Blood Pressure (mm Hg)*
122 men with fathers dead of heart disease	34.6 years	72.5 mm
878 men (overall group)	34.1 years	69.9 mm

After correction for the 0.5 year difference in age for the group with fathers dead of heart disease (a correction of 0.2mm), the difference between this group and the overall group is 72.5-70.1, or 2.4mm. While this is a small difference in mean diastolic blood pressure, the large number of cases available allows one to be sure that there is less than one chance in 100 that this difference in blood pressures would be observed as a result of random sampling Therefore there is a low degree of positive association of elevation of diastolic blood pressure in the offspring with the history of death of the father of heart disease. The magnitude of the effect is certainly less than that observed for the Atherogenic Index.

The evidence presented here is strong that a positive association exists between two known factors predisposing to coro-

or environmental mechanism, or some combination thereof, cannot be determined within the framework of this evidence.

The 122 men with a paternal history of death from heart disease smoked, on the average, 10.1 cigarettes per day. The overall group smoked, on the average, 9.9 cigarettes per day. Therefore, there is *no* evidence that would suggest that any of the association between lipoprotein level elevation and paternal history of heart disease is at all mediated by a tendency to smoke cigarettes.

THE PRACTICAL CLINICAL IMPLICATION OF ASSOCIATION OF ATHEROGENIC INDEX VALUES WITH FAMILY HISTORY OF HEART DISEASE

That a parental history of heart disease is associated with a significant elevation in Atherogenic Index value and to a lesser extent in diastolic blood pressure in offspring can now be accepted as well documented. Therefore, there is every reason to expect a higher incidence of coronary heart disease in persons whose parents had heart disease at a relatively early age than in persons without such a parental history. Further, from the data relating Atherogenic Index and blood pressure to risk of future coronary heart disease, the precise extent to which a positive family history increases the average risk of coronary heart disease in offspring could readily be estimated. Unfortunately, however, no really satisfactory unbiassed data are available to determine directly how large this association is in the population-at-large. Thus, while a higher incidence rate of coronary heart disease is definitely to be expected in the offspring of persons with heart disease, it is not possible at this time to state whether or not the Atherogenic Index plus blood pressure findings account for the totality of such association as does exist. In any event the evidence for the effect of family history operating via these mechanisms is solidly based and free of speculation or bias. The available evidence does not allow for a statement that no other possible mechanisms might exist in addition although no comparably documented evidence supports such other possible mechanisms. One possible factor that has been suggested by several workers

of a family environment that leads to smoking. For overweight persons, there does exist an average elevation in Atherogenic Index arising primarily from an association of overweight with S_f20-100 and S_f100-400 lipoprotein levels. For cigarette smokers the most prominent effect upon Atherogenic Index arises through the association of cigarette smoking with elevation of S_f0-12 lipoprotein levels.

The elevation in Atherogenic Index in the 122 men who reported the father dead of heart disease is predominantly associated with elevation in S_f20-100 and S_f100-400 lipoprotein levels. The smaller degree of elevation of S_f0-12 lipoprotein levels could not be proved significant within the existing data. These findings suggest that it would be worthwhile to know whether these 122 men are overweight relative to the overall group, and possibly whether they are heavier smokers. Degree of overweight is expressed in terms of the value known as the relative weight, which is the person's actual weight divided by the ideal weight for his height. (See Chapter IX.) The average relative weights for those with a father dead of heart disease and for the overall group of men are as follows.

For 122 men with father dead of heart disease, Relative Weight = 1.092
For 878 men in the overall 30-39 year old population sample,
Relative Weight = 1.044
Difference = 0.048

On the relative weight scale, the men whose fathers are dead of heart disease are 5% heavier than the overall group. A statistical test of this difference shows that a difference this large would arise by sampling errors less than once in 10,000 times. It can therefore be concluded that the men whose fathers died of heart disease are heavier for their height than are the men in the overall group. From the data of Table XXXII this degree of increase in relative weight would be expected, on the average, to lead to an elevation in Atherogenic Index of 2.9 units. The observed elevation for the 122 men with fathers dead of heart disease is 8.3 units. Therefore, approximately 35% of the elevation in Atherogenic Index would be expected from their degree of overweight. Whether the relationship of overweight with history of paternal death of heart disease operates via a hereditary

group whose fathers were already dead of heart disease. Inspection of these data shows immediately that in spite of the *shift in distribution* of Atherogenic Index values to high values, there are many individuals in this group characterized by low Atherogenic Index values, values lower than average for the overall population of persons of this age group. Entirely similar considerations apply to the diastolic blood pressure findings. If a person has essentially "escaped" the family history effect, namely, if he has a moderate or low Atherogenic Index and a moderate or low blood pressure value, there exists no evidence whatever that he need fear premature coronary heart disease solely because of an unfavorable family history of such disease. Even in the families characterized by one or another of the massive defects in blood lipoprotein levels, such as marked s_f0-12 lipoprotein elevation or s_f20-400 lipoprotein elevation, an appreciable fraction of the members of the family "escape" the inherited defect. Thus, when a father shows the lipoprotein derangement, it is common to find that a daughter may show the derangement too, but that one or more sons do not. Alternatively a son or several sons may show the derangement whereas none of the daughters show it

The crucial clinical issue in all of this is that the physician can be, if he chooses, vastly more precise in his prognostic evaluation of the meaning of an unfavorable family history of heart disease in a particular patient. It is neither correct medically nor good clinical medicine to issue a poor prognosis for future coronary heart disease risk to a patient simply because of an adverse family history It is not correct to inform a patient that his outlook is unfavorable "because he has chosen his ancestor's unwisely" Many such persons have far lower risks of future coronary heart disease than the "average" man in the population and this most favorable news can be transmitted to such a person by the physician who utilizes the modern, simple methods of obtaining the requisite information.

Nor should errors of the opposite type be made clinically. It does follow, from the evidence at our disposal, that a favorable family history of freedom from premature heart disease means, *on the average*, a lower risk of future coronary heart

is the inheritance of some type of defective coronary vascular tree in persons with a positive family history of early coronary heart disease. Suggestions have been made that either the intimal thickness of the coronary arteries or anatomical pecularities such origin of the arteries or kinking might be hereditary predisposing factors. These are but speculations, wholly unsupported by any evidence and hence hardly deserving of consideration in the practical clinical matter of dealing with patients.

While the evidence is conclusive that a family history of heart disease does, *on the average*, predispose the offspring to coronary heart disease via the lipoprotein and blood pressure mechanisms, it cannot be stressed too much that this is an *average* predisposition. By no means does every person with a family history of premature heart disease show the elevation in Atherogenic Index or diastolic blood pressure that characterizes the group as a whole. In Table XXII is presented the distribution of Atherogenic Index values for the 122 men in the 30-39 year age

TABLE XXII

DISTRIBUTION OF ATHEROGENIC INDEX VALUES FOR 122 MEN (30-39 YEAR AGE GROUP) WHO REPORT THEIR FATHERS ARE DEAD OF HEART DISEASE

Range of Atherogenic Index Values (units)	*Number of Men Who Reported Father Dead of Heart Disease*	*Number of Men Who Report a History Other Than Father Dead of Heart Disease*
Below 40	3	53
40-49	14	107
50-59	17	148
60-69	18	138
70-79	26	121
80-89	9	86
90 99	14	46
100-109	5	18
110-119	4	16
120-129	1	6
130-139	6	2
140 or higher	5	15
TOTAL	122	756

Chapter VII

THE RELATIONSHIP OF AGE WITH CORONARY HEART DISEASE

There is no doubt whatever that the attack rate of clinical manifestations of coronary heart disease increases with increasing age in the American population, both in the male and female sex. The United States Vital Statistics reproduced below in Table XXIII, clearly indicate the startling and definite rise in incidence of clinical coronary heart disease with increasing age for both sexes. There exist in the clinical literature some erroneous impressions concerning the relative frequency of coronary heart disease at various ages. Thus, from the analysis of the age distribution of cases of myocardial infarction in office practice or in consecutive hospital admissions, many authors have commented upon the fact that a particular age bracket, for example 50 to 59 years, appears to be that in which persons are especially prone to develop clinical coronary heart disease, simply

TABLE XXIII

FATAL CORONARY HEART DISEASE INCIDENCE RATE IN NUMBER OF PERSONS PER 100,000 PER YEAR IN THE UNITED STATES

(From U. S. Vital Statistics, 1949)

Age Group (years)	*Fatal Coronary Heart Disease Incidence Rate in Cases per 100,000 per persons per year*	
	Men	*Women*
35	49	11
45	200	52
55	656	205
65	1705	753

disease because of a lower *average* Atherogenic Index and diastolic blood pressure. But many individuals with an excellent family history of freedom from heart disease can and do show high Atherogenic Index and blood pressure values in spite of the average trend. Therefore re-assurance of a patient of a bright outlook for freedom from coronary heart disease simply because of a good family history represents poor clinical medicine, for it may deny the individual the opportunity to discover the basis for a seriously high risk of future coronary heart disease and to take, in time, those steps which might reduce the risk appreciably.

have had recourse to a superficial device for solving the problem of the increasing frequency of clinical coronary heart disease with increasing age. They have stated simply that coronary heart disease in the older age groups is a different disease from coronary heart disease in the younger age groups. With this statement being made equivalent to a definition, the difference in frequency of the disease between the older age group and the younger age group requires no special explanation. Actually, however recourse to such an explanation would mean that not just two diseases must be accounted for, but rather, many diseases, for the increasing frequency of coronary disease with aging operates all the way from the third decade of life up through at least the eighth decade of life. If the device is used of renaming the disease as a different entity in the older age group from that in the younger group, it would be quite appropriate to state that for every ten year age span there is a different disease with which we are dealing. Carried to extremes it could be stated that there is a different "coronary disease" at every year of life in order to explain increase in frequency with change in age. It is important to note that neither clinical nor pathological evidence suggests any significant difference in the basic picture of clinical coronary heart disease between that seen at one age and at another It is not surprising that there may be minor differences in the clinical picture of coronary heart disease in a 75 year old man from that in a 25 year old man, since physiologically there are many features that are different in men in the 75 year age group from men in the 25 year age group. The central pathological feature noted is that of coronary artery narrowing due to an accumulation of material within the intima, a feature that has been found to characterize myocardial infarction autopsy material all the way from 18 out to 80 years of age.

Before considering in detail the evidence with respect to coronary heart disease itself, some general concepts should be delineated concerning diseases which show an increasing frequency with increasing age, especially in relationship to the evaluation of factors conceivably responsible for these observed trends The basis for a disease may be primarily a factor which operates *instantaneously*. An illustration of this would be a sit-

because this age bracket contains a larger number of their cases than any other single age bracket. Such statistics are grossly misleading, for they fail to take into account the *size of the population at risk* in the various age categories. Thus, if there are many more men in the population in the age group, 50-59 years, than there are in the age group, 70-79 years, there may be more hospital admissions due to coronary disease in the 50-59 year age group than the 70-79 year age group even though the risk of coronary heart disease is much higher per thousand persons per year in the older age group. Data concerning the frequency of coronary heart disease in relationship with age can only be meaningful if they are expressed in reference to the population at risk, namely in terms of the attack rate, or the number of cases, per thousand persons at risk per year or per 100,000 persons at risk per year rather than in terms of absolute number of cases admitted in a hospital per year So well known is the relationship between increase in frequency of coronary heart disease with increasing age that many writers have in the past drawn the erroneous conclusions that age is *the* factor in the development of coronary heart disease and that coronary heart disease is an inevitable accompaniment of aging To be sure, the relationship of clinical coronary heart disease incidence with increasing age is highly impressive, but it by no means justifies the statement that age is *the* factor or the most important factor involved, nor does it justify a concept of the inevitability of development of clinical coronary heart disease with increasing age The phenomenon of occurrence of serious or fatal myocardial infarction in 35 year old men and even in 25 year old men no longer excites the special interest that it once did, for we now know that many men develop such serious disease even before the age of 35 years The recent experience of Yater (during World War II) in accumulating a series of over 800 documented cases of myocardial infarction in men between the ages of 18 and 39 years is eloquent testimony to the all-too-great frequency of coronary heart disease even at relatively early ages

The increasing frequency of coronary heart disease with increasing age demands explanation in an over-all concept of the nature of the evolution of this important clinical entity. Some

increased. This is true simply because for a process which operates by accumulation over time there would be a greater *accumulation* of the sub-clinical disease in 20 years than there would be in ten years, in 30 years a still greater accumulation, and in 40 years an even greater accumulation. In a hypothetical case such as this it would be wholly incorrect to make the statement that the blood sugar level had not been important in the development of the disease simply because its average level remained the same with increasing age. It could very well be the total or predominant cause of the disease. As a general procedure for demonstrating that a factor which operates in this particular manner is important for a disease, a group of individuals all at a particular age can be studied. If it is found that those who show the higher levels of the particular factor have more of the disease under consideration than do those who show low levels, this would represent strong evidence to implicate the level of the factor in the disease

The application of simple logic will often enable one to determine the manner in which a particular factor is associated with a particular disease and indeed to determine whether or not one is dealing with an *instantaneous* or an *accumulative* type of factor It is often readily possible to show that particular factors cannot possibly operate in one of the two ways, e g., as an instantaneous factor, because assumption that it does would lead to results highly inconsistent with observational material, which of course (if properly observed) must be correct. At times, it may not be possible from a single item of evidence to make the determination of whether an instantaneous factor or an accumulative factor is at hand, but with consideration of several segments of the evidence a consistent picture may emerge for one type of factor, e g the accumulative one, but a highly inconsistent picture for the other, e g., the instantaneous one, in which case the choice of the nature of the factor becomes quite clear—at least quite clear as a working hypothesis for further consideration.

The specific problem of sub-clinical and clinical coronary heart disease may now be considered in the light of these general principles The detailed evidence that the lipoprotein-Atherogenic Index and the blood pressure are two major factors

uation where an acutely toxic substance is ingested and instantaneously produces clinical manifestations. In this case there would be no accumulation of illness over previous weeks, months, or years. A second possible type of illness would be that where some factor operates, not instantaneously, but rather over a period of time. With longer periods of time passed the greater is the accumulation of the sub-clinical aspects of the disease and hence the greater the chance of expression of the disease in clinical form. In this latter case the factor responsible can be considered to be expressive of the *rate* at which sub-clinical disease accumulates, whereas the total *amount* of accumulated disease would be expressed by the multiplication of this rate factor and the time period over which it has operated. Lastly, in a complex disease process, there might be a combination of those factors which operate instantaneously and those factors which operate over a period of time to produce accumulation of disease at the sub-clinical level If a factor operates instantaneously in the production of a disease, explanation of an increasing frequency of this disease with increasing age would require that there must either be, if the factor is a presence-versus-absence factor, a progressively greater number of individuals in the population who possess this factor as age increases, or if the factor is universally present but at different levels in different individuals, there must be a sufficient increase in the percentage of individuals with high levels of this factor with increasing age in order to explain the age trends observed. On the other hand, for a factor which is expressive of the *rate* at which sub-clinical disease develops, it is possible for both the level of the factor and the fraction of the population characterized by each such level to remain constant over the entire usual life span of individuals and still be consistent with an increasing trend of mortality from the disease with increasing age. Thus, for example, *if* the level of blood sugar were known to have the same distribution and the same average level for every age in life and *if* it were also known that the level of blood sugar were expressive of the rate at which some disease develops sub-clinically, it would be expected that the overt expression of that disease would increase with increasing age even though the blood sugar level remained the same as age

that (1) the Atherogenic Index *cannot* operate primarily as an instantaneous type of factor, (2) that it would be consistent with the observed facts to consider the possibility that the Atherogenic Index operates as an *accumulative* type of factor and (3) the possibility deserves consideration that the Atherogenic Index may still operate as an instantaneous factor but some unknown, hypothetical, undiscovered factor operates as a major accumulative factor. Attention may now be turned to the blood pressure as a factor with demonstrated ability to predict the risk, or attack rate, of clinical coronary heart disease. Does the blood pressure operate as an instantaneous factor in producing risk of clinical coronary heart disease or as an accumulative factor? In Table XIV is presented the relative risk, or attack rate, of coronary heart disease for various values of the diastolic blood pressure. In order to explain a 35-fold increase in coronary heart disease attack rate that is observed for 65 year old men versus 35 year old men it would be required that the average diastolic blood pressure for 65 year old men be much higher than 150 mm Hg compared with the average of 71 mm Hg for 35 year old men. This, however, is clearly not the case since the blood pressures are 76 mm Hg and 71 mm Hg for the two age groups, respectively. Therefore, it is clearly inconsistent with reality to assume that blood pressure *can* be operating as an instantaneous factor to explain the difference in attack rate of coronary heart disease for these two age groups assuming the blood pressure to operate as the only or major factor in determining the risk. The conclusions we can draw from this are: (1) the blood pressure cannot possibly be described as an *instantaneous* factor to explain the marked increase in coronary heart attack rate with increasing age (2) it would be consistent with the evidence for the blood pressure to operate in an accumulative fashion producing the risk of clinical coronary heart disease; and (3) it would still be consistent that the blood pressure operates instantaneously but that some unknown, hypothetical, undiscovered factor oprates in an accumulative fashion Lastly the possibility must be considered that in some way the blood pressure and the Atherogenic Index might together represent an instantaneously operating factor in the production of risk of clinical coronary heart dis-

in determining the risk of clinical coronary heart disease has been presented. Indeed no other factors have yet been discovered for which positive evidence exists demonstrating an association with the risk of future clinical coronary heart disease that cannot be explained either by their effect on the Atherogenic Index values or by their effect on the blood pressure. This is not to say that no other independent factors will ever come to light. However, it would be highly pertinent, when and if any such factor is proposed, to determine carefully whether it represents a truly new and independent factor or whether it is simply another reflection of the action of the blood lipoproteins and/or the blood pressure. It is highly pertinent to evaluate serially both the lipoprotein-Atherogenic Index value and the blood pressure with respect to operation either as instantaneous factors or as accumulative factors.

The risk of clinical coronary heart disease, or the attack rate of clinical coronary heart disease, for various values of the Atherogenic Index in 35 year old men is presented in Table XV. From the U. S. Vital Statistics the separate knowledge is available showing that the coronary heart disease attack rate for 65 year old men is approximately 35 times that for 35 year old men. If the Atherogenic Index value were to be an instantaneously operating factor in determining the risk of coronary heart disease and were the only, or major, factor operating, it should be possible, by inspection of the risk table for 35 year old men, Table XV, to determine how high the average Atherogenic Index would have to be in 65 year old men in order to account for this 35-fold increase in heart attack rate. It is seen that an Atherogenic Index value of more than 150 units would be required for the average 65 year old man if the Atherogenic Index operated as an instantaneous factor and were the only one of consequence. However, studies of numerous samples of the population indicate that the average Atherogenic Index value in 65 year old men is only 68.8 units. This is vastly below the required value of over 150 units. Indeed the Atherogenic value of 68 8 units would give rise to a prediction of no increase in heart attack rate for 65 year old men versus 35 year old men, *assuming instantaneous operation.* Therefore the conclusions must be drawn

that (1) the Atherogenic Index *cannot* operate primarily as an instantaneous type of factor, (2) that it would be consistent with the observed facts to consider the possibility that the Atherogenic Index operates as an *accumulative* type of factor and (3) the possibility deserves consideration that the Atherogenic Index may still operate as an instantaneous factor but some unknown, hypothetical, undiscovered factor operates as a major accumulative factor Attention may now be turned to the blood pressure as a factor with demonstrated ability to predict the risk, or attack rate, of clinical coronary heart disease. Does the blood pressure operate as an instantaneous factor in producing risk of clinical coronary heart disease or as an accumulative factor? In Table XIV is presented the relative risk, or attack rate, of coronary heart disease for various values of the diastolic blood pressure. In order to explain a 35-fold increase in coronary heart disease attack rate that is observed for 65 year old men versus 35 year old men it would be required that the average diastolic blood pressure for 65 year old men be much higher than 150 mm Hg compared with the average of 71 mm Hg for 35 year old men. This, however, is clearly not the case since the blood pressures are 76 mm Hg and 71 mm Hg for the two age groups, respectively. Therefore, it is clearly inconsistent with reality to assume that blood pressure can be operating as an instantaneous factor to explain the difference in attack rate of coronary heart disease for these two age groups assuming the blood pressure to operate as the only or major factor in determining the risk. The conclusions we can draw from this are· (1) the blood pressure cannot possibly be described as an instantaneous factor to explain the marked increase in coronary heart attack rate with increasing age, (2) it would be consistent with the evidence for the blood pressure to operate in an accumulative fashion producing the risk of clinical coronary heart disease; and (3) it would still be consistent that the blood pressure operates instantaneously but that some unknown, hypothetical, undiscovered factor oprates in an accumulative fashion Lastly the possibility must be considered that in some way the blood pressure and the Atherogenic Index might together represent an instantaneously operating factor in the production of risk of clinical coronary heart dis-

ease. In Chapter V an explanation was given of how one can calculate the risk of clinical coronary heart disease by multiplying together the independent risks from the blood pressure data and from the Atherogenic Index data. We may now consider the case of 35 year old men versus 65 year old men using the products of the two independent risks from the blood pressure and from the Atherogenic Index. It is seen that using the mean values for diastolic blood pressure and Atherogenic Index for 65 year old men versus 35 year old men that the attack rate for 65 year old men would be approximately the same as the attack rate for 35 year old men which is far below the relative attack rates actually observed. Hence the net conclusion that can be drawn from the blood pressure alone, the Atherogenic Index *alone, or a risk accrued from their combination is that neither* of these values alone nor their combination could possibly operate as instantaneous factors in determining coronary heart disease risk. It would still be consistent to consider the possibility that either alone or the two together operate as accumulative types of factors in determining the coronary heart disease risk or that some wholly undiscovered, unmeasured, unknown and hypothetical factor accounts for the age effect in coronary heart disease. Inasmuch as neither alone nor these two factors in combination could consistently explain the observed fact of the age increase of coronary heart disease risk operating as instantaneous factors, attention may be turned to the credibility that either or both may operate as accumulative factors in determination of risk. Before proceeding with this, a major point of scientific method and philosophy must be stated. When evidence is clearly at hand that a given factor is definitely associated with a disease, as such evidence is clearly at hand both for the Atherogenic Index and for the blood pressure with coronary heart disease, it is completely illogical to abandon the test of whether instantaneous operation or accumulative operation of such factors can explain the observed data and to jump immediately to the possibility of a third unknown, hypothetical, undemonstrated, unmeasured factor. It behooves the investigator, as a first step, to test both the instantaneous and the accumulative possibilities for those factors which are known and proven It is only when

and if the factors which are known and proven cannot possibly explain the observations either on an instantaneous or an accumulative basis that some additional factor must be sought. This point continues to escape many investigators. Nature is complicated enough not to require that scientists and medical investigators introduce *needless* additional complications in her understanding. The evidence may be evaluated in these lights, "Is there any inconsistency with observational data if the Atherogenic Index and the diastolic blood pressure are considered as accumulative factors in coronary heart disease risk, and is there ancillary supportive evidence which suggests that such factors do or do not operate as accumulative factors?"

THE ATHEROGENIC INDEX CONSIDERED AS AN ACCUMULATIVE FACTOR

It has been shown that the Atherogenic Index factor cannot operate as an instantaneous factor. Would consistency with observational material be achieved by postulation that the Atherogenic Index operates as an accumulative factor? Suppose that the Atherogenic Index value of a person operates as an accumulative factor Under such circumstances one would expect that a particular Atherogenic Index operating for two years would accumulate twice as much toward the risk of coronary heart disease as that same Atherogenic Index operating over one year. Correspondingly, that same Atherogenic Index operating for ten years would accumulate ten times as much toward the risk of coronary heart disease as if such an Atherogenic Index had been operating for only one year The corollary of such reasoning concerning accumulative operation would be that an Atherogenic Index of 150 units will accumulate twice as much toward the risk of coronary heart disease in one year as an Atherogenic Index of 75 units, and correspondingly that an Atherogenic Index of 150 units would accumulate as much in one year as an Atherogenic Index of 75 units would accumulate in two years. Later we will come to discussions of possible more refined modifications of the handling of the time variable, but for the moment this is an adequate approach In Chapters III and V it was

shown (Tables I and XV) that for any particular age group, such as 30-39 year old males, that the Atherogenic Index is markedly increased for those who develop clinical coronary heart disease over those who do not and that there is a rising risk of coronary heart disease with rising Atherogenic Index values. For example, at Atherogenic Index values of 150 units, the future risk of coronary heart disease, or the attack rate of coronary heart disease in cases per thousand per year, will be approximately *11.2 times that for an Atherogenic Index of 75 units.*

Would the accumulative operation of Atherogenic Index help explain the marked increase in coronary heart disease in 65 year old men in terms of numbers of cases per thousand per year as compared with 35 year old men? For purposes of evaluation of this concept one can start with simplifying assumptions, and then determine how the concept would be modified by reducing the simplifications. If 75 units of Atherogenic Index operating over two years amounts to the same accumulation of risk as 150 units operating over one year, such reasoning could be extended to state that 75 Atherogenic Index units operating for ten years would give rise to a total accumulation of 750 units, for twenty years to 1500 units, for thirty years, to 2250 units, and for forty years to 3000 units Now let us (for simplification) assume that the average man at age 35 years has had an Atherogenic Index value of 69.7 units for all the 35 years of his life and correspondingly let us assume that the average 65 year old man who has an Atherogenic Index of some 68.8 units had that same value for all of his life. The 35 year old man with an Atherogenic Index of 69.7 units operating over 35 years would have accumulated 35x69.7 or 2,440, units toward his risk of coronary heart disease. The 65 year old average man with a value of 68.8 units operating over 65 years would have accumulated 4,472 units in toto. Now how do these two respective values of the number of accumulated units rate in terms of expected risk of coronary heart disease. This can be approximated by reference to 35 year old men If a man were to accumulate 4,472 units (which is the value for the *average* 65 year old man) in 35 years instead of 65 years, he would have had to have an Atherogenic Index value of 4,472 divided by 35, or 127.8 units The

risk tables (Table XV) show that in 35 year old men an Atherogenic Index of 127.8 units corresponds to 33.3 over 3.77, or 8.8 times as high a risk as for the average 35 year old man with an Atherogenic Index of 69.7 units. Thus, whereas consideration of the Atherogenic Index as an instantaneous factor leads to prediction of nearly equal risks for the average 35 year old man and the average 65 year old man, the accumulation concept in its simplest form predicts an 8.8 fold higher risk for the 65 year old man, which is much closer to reality. It is important now to go back to the simplifying approximations that have been applied. It can be demonstrated readily that the simplifying approximations have in no way materially altered the results obtained through the concept of accumulation. One of the simplifying approximations made is that the man at 35 years of age with an Atherogenic Index of 69.7 units had this same Atherogenic Index all through the first 35 years of life. It was also approximated

TABLE XXIV

AGE TRENDS IN MEAN ATHEROGENIC INDEX VALUES FOR UNITED STATES MALES AND FEMALES

Age (years)	*Atherogenic Index (in units)* *Males*	*Females*
Birth	(49)	(40)
5	(49)	(40)
10	(49)	(40)
15	49.5	40.5
20	51.5	41.0
25	58.0	44.7
30	64.3	48.6
35	69.7	52.3
40	75.6	55.5
45	79.8	58.5
50	79.7	61.9
55	76.5	64.8
60	73.0	67.3
65	68.8	69.5
70	61.7	71.7

Values in parenthesis are based upon fewer than 25 cases. Hence these values are not stably fixed.

that the 65 year old man with an Atherogenic Index of 68.8 units had this same Atherogenic Index value throughout his entire 65 years. Neither of these approximations could possibly hold for every man in the population for this would mean that the average Atherogenic Index does not change with age. But from direct observation it is known that the average Atherogenic Index does change with age (see Table XXIV). It was shown (Chapter V) that persons tend very strongly to retain their *relative* ranking on the Atherogenic Index scale over a period of years throughout adult life. Thus a 20 year old becoming a 22 year old tends to remain as much above or below average in Atherogenic Index as he was at age 20. Similarly, a 30 year old becoming a 32 year old, a 40 year old becoming a 42 year old, *and a 50 year old becoming a 52 year old, all tend to retain* their positions relative to persons of the same age categories on the Atherogenic Index scale, assuming they do not change markedly in weight or develop some disease such as diabetes, hypothyroidism, or nephrosis. Therefore the first simplifying approximation, that the Atherogenic Index for a 35 year old man is the same for all the 35 years of his life, may be substituted by an approximation which is extremely close to the truth because of the fact that people retain their relative ranking throughout life. This close approximation would be that a man who at age 35 is average in Atherogenic Index would have had an average value of the Atherogenic Index for all periods in life before that. The *trend in Atherogenic Index values from childhood through the* 8th decade of life is known from direct measurement (See Table XXIV) Therefore if the average 35 year old man shows an Atherogenic Index value of 69.7 units, then at 30 years of age his Atherogenic Index would have been 64.3 units, at 25 years, 58.0 units, at 20 years, 51.5 units, at 15 years, 49.5 units, at 10 years, 49 units, and approximately that same value back to the time of birth. Now the total accumulation toward risk of coronary heart disease can be caculated directly This is done by considering successive five year intervals from birth out to the age of 35 years.

For the interval, 0-5 years of age,
Average Atherogenic Index = 49 units, Accumulation is 5x49 = 245 0

For the interval 5-10 years of age, Average Atherogenic Index = 49 units,	Accumulation is 5x49 = 245.0
For the interval 10-15 years of age, Average Atherogenic Index = 49.2 units,	Accumulation is 5x49.2 = 246.0
For the interval 15-20 years of age, Average Atherogenic Index = 50.5 units,	Accumulation is 5x50.5 = 252.5
For the interval 20-25 years of age, Average Atherogenic Index = 54.8 units,	Accumulation is 5x54.8 = 274.0
For the interval 25-30 years of age, Average Atherogenic Index = 61.1 units,	Accumulation is 5x61.1 = 305.5
For the interval 30-35 years of age, Average Atherogenic Index = 67.0 units,	Accumulation is 5x67.0 = 335.0

Now all these five year increments can be summed up, yielding a total accumulation=1,903 units. In an entirely similar manner, the five year increments from birth out to 65 years can be calculated and summed for the average 65 year old man, yielding 4,174 units

This arithmetic provides the total accumulation for both the average 35 year old man and the average 65 year old man, *without* the simplifying approximation of constant Atherogenic Index value throughout life. The only approximation utilized is that a person retains, on the average, his *relative* ranking on the Atherogenic Index scale throughout life, an approximation that is known from other considerations to be quite valid. For purposes of estimation of coronary heart disease risk, if the 65 year old average man had accumulated his total amount in 35 years instead of 65 years, he would have had to show a much higher Atherogenic Index value throughout those 35 years. What Atherogenic Index would he have *required* to have accumulated this total amount in 35 years? Let us set this Atherogenic Index value as x units. From the trends in Atherogenic Index with age (Table XXIV), it can be stated that the Atherogenic Index value must have been 96% of x between 30 and 35 years, 88% of x between 25 and 30 years, 79% of x between 20 and 25 years, 73% of x between 15 and 20 years, 71% of x between 10 and 15 years, 70% of x between 5 and 10 years, and 70% of x between 0 and 5 years. The total accumulation by 35 years is to be 4,174 units. Therefore the *very simple* algebraic equation can be written:

$$5(0.96x) + 5(0.88x) + 5(0.79x) + 5(0.73x) + 5(0.71x) + 5(0.70x) + 5(0.70x) = 4174.$$

Solving for x, we obtain 152.3 units, which is the Atherogenic Index value at 35 years required to produce the same total accumulation in 35 years that the average 65 year old man accumulates in 65 years. From the risk table for 35 year old men (Table XV), an Atherogenic Index of 69.7 units corresponds to a relative risk of 3.77, whereas an Atherogenic Index of 152.3 units corresponds to a relative risk of 57.8. Therefore, on the accumulation basis, the average 65 year old man has a 57.8 over 3.77, or 15.3 fold higher risk of coronary heart disease than the average 35 year old man. The model described above for Atherogenic Index operating in an *accumulative* manner predicts, therefore, a 15.3 fold higher risk of coronary heart disease in the average 65 year old man than in the average 35 year old man, whereas the *instantaneous* operation had predicted nearly equal risks for these two men. Since the *observed* relative risk (from Vital Statistics) is 34.8 fold for 65 year old men versus 35 year old men, it is clear that the accumulative model brings us enormously closer to reality than does the instantaneous model.

However, this model so far only provides consideration of the Atherogenic Index factor. In Chapter V it was shown that the true risk for any individual of development of coronary heart disease from the known factors involved is arrived at by the *multiplication* of the risk from the blood pressure by the risk from the Atherogenic Index. Therefore it is now necessary to calculate the risk due to blood pressure as above and then to calculate the combined risks from blood pressure and from Atherogenic Index on the *accumulative* basis.

THE BLOOD PRESSURE CONSIDERED AS AN ACCUMULATIVE FACTOR

The procedure for calculation of coronary heart disease risk considering diastolic blood pressure to operate on an accumulative basis is entirely analogous to that for the Atherogenic Index. If the diastolic blood pressure operates in an accumulative fashion, then total accumulation toward risk is calculated by multiplying the diastolic blood pressure by the number of years during which that blood pressure has existed. The average blood pres-

sure trends with age from birth out to the eighth decade of life are available (Table XXV). Thus for the average 35 year old man with a diastolic blood pressure of 71.0 mm Hg, the average pressure between 30 and 35 years would have been 70.1 mm Hg, between 25 and 30 years, 68.3 mm Hg, between 20 and 25 years, 66.5 mm Hg, between 15 and 20 years, 63.7 mm Hg, between 10 and 15 years, 61.4 mm Hg, between 5 and 10 years, 60.5 mm Hg and between 0 and 5 years, 60.0 mm Hg. The total accumulation toward coronary disease risk for the average 35 year old man would, therefore, be 70.1x5 + 68.3x5 + 66.5x5 + 63.7x5 + 61.4x5 + 60.5x5 + 60.0x5, or 2,253 units in toto. The same type of arithmetic for the average 65 year old man yields a total accumulation of 4,482 units. If the 65 year old man were to have accumulated this total amount in 35 years instead of 65 years, he would have had to have had a much higher diastolic blood pressure at 35 years of age. What diastolic blood pressure would have been required? This is readily

TABLE XXV

DIASTOLIC BLOOD PRESSURE TRENDS WITH AGE FOR UNITED STATES MALES AND FEMALES

Age (in years)	*Diastolic Blood Pressure (in mm Hg)* Males	Females
Birth	(60.0)	(60.0)
5	60.0	(60.0)
10	60.9	60.0
15	61.9	61.0
20	65.5	63.5
25	67.5	63.9
30	69.2	64.6
35	71.0	65.5
40	72.6	68.1
45	74.0	70.5
50	74.7	74.6
55	75.3	75.3
60	75.8	77.7
65	76.0	79.8
70	75.8	81.8

Values in parenthesis are estimated from fewer than 25 cases. They are hence not stably fixed.

calculated by the same methods utilized for the Atherogenic Index. The requisite blood pressure value may be designated as x mm Hg. From the age trends in diastolic blood pressure values (Table XXV) the blood pressure between 30 and 35 years of age would have been (0.99x) mm Hg, between 25 and 30 years, (0.96x) mm Hg, between 20 and 25 years, (0.94x) mm Hg, between 15 and 20 years, (0.90x) mm Hg, between 10 and 15 years, (0.86x) mm Hg, between 5 and 10 years, (0.85x) mm Hg, and between 0 and 5 years, (0.84x) mm Hg. The total accumulation toward risk must be set equal to 4,482 units. Therefore, this simple algebraic equation holds:

$$(0.99x) \times 5 + (0.96x) \times 5 + (0.94x) \times 5 + (0.90x) \times 5$$
$$+ (0.86x) \times 5 + (0.85x) \times 5 + (0.84x) \times 5 = 4482$$

Solving for x, we obtain 141.4 mm Hg as the diastolic blood pressure required for the average 65 year old man to have accumulated as much in 35 years as he does at his actual diastolic blood pressure in 65 years. From Table XIV relating blood pressure value to risk of coronary heart disease, it is seen that a blood pressure of 71.0 mm Hg corresponds to a risk of 2.25, whereas a blood pressure of 141.4 mm Hg corresponds to a risk of 11.8. Therefore, on the accumulative basis of operation of the blood pressure factor, the predicted risk for the average 65 year old man is 11.8 over 2.25, or 5.24 times that for the average 35 year old man. This is to be contrasted with the relative risk of 3.43 over 2.25, or 1.5 times, estimated for the diastolic blood pressure operating as an *instantaneous* factor. It is clear that the accumulative operation of blood pressure provides a relative risk estimate much more in accord with observational data (The Vital Statistics) than does instantaneous operation of the blood pressure.

THE COMBINED RISK OF CORONARY HEART DISEASE WITH BOTH ATHEROGENIC INDEX AND DIASTOLIC BLOOD PRESSURE CONSIDERED AS ACCUMULATIVE FACTORS

Since the overall risk of coronary heart disease is obtained by multiplying the risk arising from the Atherogenic Index by that arising from the diastolic blood pressure, it is now appro-

priate to estimate this overall risk from the estimates for each of these factors operating in an accumulative manner. The Atherogenic Index, operating as an accumulative factor, leads to a predicted risk for 65 year old men 15.3 times that for 35 year old men. The diastolic blood pressure, operating as an accumulative factor, leads to a predicted risk for 65 year old men 5.24 times that for 35 year old men. Multiplying 15.3 by 5.24 yields a combined, or overall, risk for 65 year old men 80.2 times that for 35 year old men. Proceeding along similar lines, the expected comparison in fatal coronary heart disease rate for 45 and 55 year old men with that for 35 year old men can be calculated, with Atherogenic Index and blood pressure operating as accumulative factors. All these evaluations plus the observational information from Vital Statistics are presented in Table XXVI. These comparisons show that this first approximation to a model of accumulative operation of Atherogenic Index and diastolic blood pressure provides predicted ratios for one age group of men compared with another age group within a factor of 2 to 2.5 of the observed ratios from U. S. Vital Statistics. This is to be contrasted with the gross inconsistency of being approximately a factor of 35 times away from observation when the two factors are considered to operate as instantaneous ones. Clearly, accumulative operation provides an answer enormously closer to *reality*. The fact that accumulative operation is still approximately a factor of 2 or 2.5 off from observation is hardly dis-

TABLE XXVI

COMPARISON OF FATAL CORONARY HEART DISEASE INCIDENCE RATES FROM PREDICTION BASED UPON ACCUMULATIVE OPERATION OF ATHEROGENIC INDEX AND DIASTOLIC PRESSURE WITH OBSERVATIONAL DATA FROM U. S. VITAL STATISTICS

(MALES)

Age Groups Under Comparison	*Predicted Ratio of Fatal Coronary Disease Attack Rates*	*Observed Ratio of Fatal Coronary Disease Attack Rates (U. S. Vital Statistics)*
65 years versus 35 years	80.2	34.8
55 years versus 35 years	34.9	13.4
45 years versus 35 years	9.4	4.1

calculated by the same methods utilized for the Atherogenic Index. The requisite blood pressure value may be designated as x mm Hg. From the age trends in diastolic blood pressure values (Table XXV) the blood pressure between 30 and 35 years of age would have been (0.99x) mm Hg, between 25 and 30 years, (0.96x) mm Hg, between 20 and 25 years, (0.94x) mm Hg, between 15 and 20 years, (0.90x) mm Hg, between 10 and 15 years, (0.86x) mm Hg, between 5 and 10 years, (0.85x) mm Hg, and between 0 and 5 years, (0.84x) mm Hg. The total accumulation toward risk must be set equal to 4,482 units. Therefore, this simple algebraic equation holds:

$$(0.99x) \times 5 + (0.96x) \times 5 + (0.94x) \times 5 + (0.90x) \times 5$$
$$+ (0.86x) \times 5 + (0.85x) \times 5 + (0.84x) \times 5 = 4{,}482$$

Solving for x, we obtain 141.4 mm Hg as the diastolic blood pressure required for the average 65 year old man to have accumulated as much in 35 years as he does at his actual diastolic blood pressure in 65 years. From Table XIV relating blood pressure value to risk of coronary heart disease, it is seen that a blood pressure of 71.0 mm Hg corresponds to a risk of 2.25, whereas a blood pressure of 141.4 mm Hg corresponds to a risk of 11.8. Therefore, on the accumulative basis of operation of the blood pressure factor, the predicted risk for the average 65 year old man is 11.8 over 2.25, or 5.24 times that for the average 35 year old man. This is to be contrasted with the relative risk of 3.43 over 2.25, or 1.5 times, estimated for the diastolic blood pressure operating as an *instantaneous* factor. It is clear that the accumulative operation of blood pressure provides a relative risk estimate much more in accord with observational data (The Vital Statistics) than does instantaneous operation of the blood pressure.

THE COMBINED RISK OF CORONARY HEART DISEASE WITH BOTH ATHEROGENIC INDEX AND DIASTOLIC BLOOD PRESSURE CONSIDERED AS ACCUMULATIVE FACTORS

Since the overall risk of coronary heart disease is obtained by multiplying the risk arising from the Atherogenic Index by that arising from the diastolic blood pressure, it is now appro-

over a period of time in order to result in the accumulation of visibly evident lesions. In all the experimental animal studies which have been done over the years on the development of a lesion somewhat analogous to the human lesion of intimal arteriosclerosis, it has been noted that, where blood lipoprotein, or lipid, elevation is utilized to produce the lesion, the lesions do not develop instantaneously but rather require *time* to develop. Furthermore, the longer the lipoprotein elevation has existed the more extensive is the development of the lesions. Similarly, with respect to the blood pressure factor, the work of Heptinstall and co-workers showed clearly that, for a particular blood lipid elevation, the extent to which lesion development was aggravated by the existence of hypertension was greater the longer the period of maintenance of elevated blood pressure, cogent evidence for the accumulative operation of the blood pressure factor. It is important to repeat here that such pathological considerations are in no way being utilized as the prime basis for the accumulation concept The general thesis rests upon its own merits specifically in connection with the problem of human coronary heart disease It is reassuring to find the concept in excellent agreement with the human pathological and experimental animal evidence

THE PRACTICAL CLINICAL IMPLICATIONS OF THE ACCUMULATIVE OPERATION OF ATHEROGENIC INDEX AND BLOOD PRESSURE IN CORONARY HEART DISEASE

Since the evidence is extremely strong that the Atherogenic Index and the blood pressure factors operate over a period of time to increase *the risk of future* clinical coronary heart disease, or to accumulate what may be referred to as additional *sub clinical* coronary heart *disease*, this evidence must be reckoned with in appraising the clinical approach to the patient. As an illustration, suppose that a group of 20-25 year old males is being evaluated as part of a general adult screening program for assessment of the risk of *future clinical* coronary heart disease A small percentage of these 20-25 year old men will show

turbing, considering the several places in this first approximation to a model that can produce some error in prediction. It is likely that refinements both in the data available (including the U. S. Vital Statistics) and in the model itself may eliminate even the remaining discrepancy.

In problems such as this not only is it pertinent to examine whether accumulative versus instantaneous operation gives better consistency with actual observations with respect to one phenomenon (here, risks of fatal coronary heart disease) *but also* the evidence must be viewed in an over-all light with respect to reasonableness. There exists a large mass of additional information which argues strongly in favor of the accumulative mode of operation both of the Atherogenic Index and of the blood pressure rather than the instantaneous mode of operation. For example, there are the phenomena surrounding the difference in corornary heart disease incidence rate between men and women, phenomena which will be treated in extensive detail in the next chapter. However, it can be stated here that the only reasonable way in which the differences in heart attack rate between men and women can be explained in terms of the findings for the Atherogenic Index and the blood pressure is via accumulative operation rather than via instantaneous operation. To return to pathological consideration (although as repeatedly emphasized in this book no special support for the over-all concept is required from pathological considerations), two entities may be considered, first, xanthomatosis in humans and second, arteriosclerosis development in experimental animals. In families *demonstrating the lesion of xanthomatosis it is found* that some young members of these families show the same degree of lipoprotein elevation as do other members of the family, such as, for example, their parents The parents have fully developed, large xanthomatous lesions while the younger members in the family may have minimal lesions or none at all. Follow-up of this phenomenon by Piper and Orrlid[34] has shown that this is a matter of passage of time. If the younger members are followed over a period of time they do develop xanthomatous lesions This is direct evidence, for a lesion similar to that of arteriosclerosis, which indicates that high lipoprotein levels must *operate*

over a period of time in order to result in the accumulation of visibly evident lesions. In all the experimental animal studies which have been done over the years on the development of a lesion somewhat analogous to the human lesion of intimal arteriosclerosis, it has been noted that, where blood lipoprotein, or lipid, elevation is utilized to produce the lesion, the lesions do not develop instantaneously but rather require *time* to develop. Furthermore, the longer the lipoprotein elevation has existed the more extensive is the development of the lesions Similarly, with respect to the blood pressure factor, the work of Heptinstall and co-workers showed clearly that, for a particular blood lipid elevation, the extent to which lesion development was aggravated by the existence of hypertension was greater the longer the period of maintenance of elevated blood pressure, cogent evidence for the accumulative operation of the blood pressure factor. It is important to repeat here that such pathological considerations are in no way being utilized as the prime basis for the accumulation concept The general thesis rests upon its own merits specifically in connection with the problem of human coronary heart disease It is reassuring to find the concept in excellent agreement with the human pathological and experimental animal evidence

THE PRACTICAL CLINICAL IMPLICATIONS OF THE ACCUMULATIVE OPERATION OF ATHEROGENIC INDEX AND BLOOD PRESSURE IN CORONARY HEART DISEASE

Since the evidence is extremely strong that the Atherogenic Index and the blood pressure factors operate over a period of time to increase the risk of *future* clinical coronary heart disease, or to accumulate what may be referred to as additional sub clinical coronary heart disease, this evidence must be reckoned with in appraising the clinical approach to the patient. As an illustration, suppose that a group of 20-25 year old males is being evaluated as part of a *general* adult screening program for assessment of the risk of future clinical coronary heart disease A small percentage of these 20-25 year old men will show

extremely high Atherogenic Index values. Such Atherogenic Index values imply a risk of coronary heart disease for these men which is extremely high compared to that for those 20-25 year old men who have low Atherogenic Index values. Such relative risk may be in the neighborhood of 5, 10, 15, or 30 times as high for the men with very high Atherogenic Index values as for men with very low Atherogenic Index values. In spite of this, clinically the conclusion should not be drawn that these men are all going to expire immediately from coronary heart disease. For some strange reason certain workers who do not appear to understand the entire problem clearly seem to regard the fact that such men do *not* immediately drop dead of coronary heart disease as being in itself testimony adequate to refute the entire body of evidence concerning blood lipids and their relationship to coronary heart disease. Indeed precisely the opposite is the correct expectation. In spite of the marked elevation of the Atherogenic Index in such young individuals and of the fact that 30 men with high Atherogenic Index values will die of coronary heart disease in any specified time period for every one with a very low Atherogenic Index who dies of coronary heart disease in that same time period, it is still true that the vast majority of the 25 year old men with high Atherogenic Index values will be alive in one year, in five years, and even in ten years This is true simply because it takes a *certain amount of time* over which very high Atherogenic Index values must operate in order to increase the risk to a point where an appreciable proportion of the men are dying per year. Indeed reasonable estimates of this phenomenon have been made[39] to determine how many of these men will die each year of clinical coronary heart disease. Listed in Table XXVII is the proportion of an original group of 35 year old men that will be dead of coronary heart disease in 1, 5, 10, 15, 20 and 25 years for very low Atherogenic Index values and for very high Atherogenic Index values. Inspection of these data indicates that even for the very high Atherogenic Index value group, at the end of 1 year well over 95% of the men still survive. The entire concept predicts that this many will survive one year simply because they have not accumulated enough risk to have a higher death rate On the other hand,

TABLE XXVII

PERCENTAGE OF MEN ESCAPING FATAL CORONARY HEART DISEASE IN RELATION TO AGE AND ATHEROGENIC INDEX VALUES

(For Men whose Atherogenic Indices are Determined at 35 years of age)

Atherogenic Index at 35 years of age	*% Alive 1 Year Later*	*% Alive 5 Years Later*	*% Alive 10 Years Later*	*% Alive 15 Years Later*	*% Alive 20 Years Later*	*% Alive 25 Years Later*
20	99 998	99 99	99 98	99 97	99 94	99 92
40	99 997	99 98	99 97	99 85	99 55	99 2
60	99 996	99 92	99 68	99 1	97 9	96.2
80	99 98	99 73	99 0	97 3	94 8	91 1
100	99 85	98 95	97.2	89.2	81.9	70 5
120	99.75	98 1	95 1	89 4	80 9	66 3
140	99.5	96 6	91.1	81.2	65 6	42 0
160	99 3	93 9	83 0	66 8	43 9	Less than 18 0
180	98 8	91.2	77 6	52 1	23 3	Less than 5 0
200	98.5	86 8	64.3	32 5	6 4	Less than 1 0

this in no way is inconsistent with the prediction that hundreds of times as many of these men will have died even in one year as is found for the men with very low Atherogenic Index values. As the accumulation goes on with passage of years at the high Atherogenic Index values, the fraction of individuals who survive begins to drop off rather sharply, such that at 25 years beyond the original evaluation it is found that over 99% of the high group (A.I. = 200 units) is expected to be dead and that the death rate per year is high. However, for the low Atherogenic Index group even 25 years later less than 1% is expected to be dead, *and the death rate per year is still comparatively low.* The clinical maxim to be derived from this is that, for a person with a very high Atherogenic Index value at a young age, the expectation is *not* that he will very shortly be dead of clinical coronary heart disease Rather, the expectation is that he has a high chance of living for several years. On the other hand, it is known that he is *accumulating coronary heart disease risk* at a markedly excessive rate compared with a person with a low Atherogenic Index value and that preventive measures are clinically indicated in order to reduce the rate at which he is accumulating such risk.

The other clinical concern that the accumulation concept must develop in the physician is that, with a high value of the Atherogenic Index and/or the blood pressure, he has evidence of a high rate of development of sub-clinical coronary heart disease, or alternatively, a high rate of accumulation of risk of future clinical coronary heart disease. Since this is an accumulative process, the time most favorable for attempting to intercept a high rate of sub-clinical coronary heart disease development is as early as possible in the over-all development so as to prevent the actual accumulation of a high amount of sub-clinical coronary disease, or to prevent the accumulative establishment of a high risk of clinical coronary heart disease. Even if at some later time the rate of accumulation were lowered, this might be somewhat late. For even if the rate of accumulation is lowered at a particular point in later life, such that *new* risk is not accumulating at a rapid rate, the fact that a long period has passed at which such risk has been building up to make the total risk high can still result in a high coronary disease death rate for such indi-

iduals. The time for clinical action *in this sphere is* therefore early in adult life.

There is one possible consideration which might alter somewhat the clinical conclusions that would be arrived at from the model of an accumulative type of development of coronary heart disease risk. This is the all-important question of the extent to which a risk, once established, can be reversed by alteration of those factors which lead to the risk. With respect to coronary heart disease, assume that, as a result of an elevated blood pressure and an elevated Atherogenic Index over a period of years, a man has accumulated a high risk of coronary heart *disease developing clinically* at any particular time in the future. What is the possibility not only that his rate of accumulation of *new* risk will be altered if he should lower his blood pressure and his Atherogenic Index, but also that the risk already accumulated may itself decrease to some extent? Another way of asking this question is, "What is the prospect that, once a certain amount of sub-clinical coronary heart disease (regarding subclinical heart disease as the accumulation of risk of the later clinical event) has developed, some of this sub-clinical *coronary heart disease is reversible?"* The precise answer *to this* question is not available at this time. If some of the ancillary evidence is sought out, for example, that pertaining to the arteriosclerotic lesion and to the xanthomatotic lesion (a lesion which undoubtedly is closely related to that which leads to an accumulation of sub-clinical coronary heart disease and to the accumulation of clinical coronary heart disease risk), some highly suggestive clues are obtained. It is known *that the* arteriosclerotic lesion in experimental animals is definitely reversible to a large extent when *the instigating* factors *are reduced in* intensity. Thus where lipoprotein elevation in experimental animals leads to the accumulation of arterial lesions, it is *known that not only do* new lesions fail to develop when the lipoprotein levels are lowered, but also that some of the accumulated lesions do show reversal and diminution in size[40] In the author's own experience with human xanthomatotic patients, in every case where lesions were developing at an appreciable rate and where large established lesions were present during the time when lipoprotein levels were

high, two phenomena accompanied a lowering in lipoprotein levels. First, new lesions failed to develop and second, old lesions already established showed marked regression and, in many cases, complete disappearance. The older the lesion, the less chance there was for its complete disappearance when the lipoprotein-lowering regimen was instituted. These are illustrations showing that, for lesions associated with coronary heart disease, the reduction in intensity of factors which determine the rate of accumulation of the lesion not only had the effect of reducing the rate of *new* accumulation but also the effect of allowing reversal mechanisms to exceed development rates, with resulting regression of established lesions. Whether or not one should translate such evidence *directly* for the case of coronary heart disease risk is immaterial The precise, possible rate of any reversal of accumulated coronary disease risk cannot be evaluated at the present time, although efforts are being made to set up models and to test concepts in this direction. Until such evidence can be clearly crystallized, and until the exact extent to which reversal of any established risk of future clinical coronary heart disease can be mitigated by altering the current accumulation is known, it would certainly seem on the side of a clinical prudence to count very little on the reversal of already established risk. Every energy should therefore be centered upon the earliest possible lowering of the rate of accumulation of *new* risk. It should be obvious that, if one starts with 60 year old men to determine whether they have a high risk of coronary heart disease as a result of an elevation in Atherogenic Index and an elevation in blood pressure, they have had a very long period of years in which high levels may have operated and hence have contributed to an already-existing large risk of *clinical coronary heart disease*. Therefore, while it would certainly be reasonable to attempt to reduce the rate of accumulation of new risk in such men, it should also be expected that, even for a regimen which lowers the Atherogenic Index drastically and which lowers the blood pressure to a very satisfactory range, many such men will still go on to develop clinical and fatal coronary heart disease as a result of their *already-accumulated high risk*. If 50 year old men with the same Atherogenic Index and blood pressure values

are considered, the outlook is more favorable, since they have had ten fewer years in which to accumulate risk due to these high values. It would be clinically very helpful to apply preventive medicine for 50 year old men rather than for 60 year old men Extension of such reasoning makes it quite obvious that if men have already identified themselves at least with respect to one of these factors, the Atherogenic Index, by the time they are in their twenties, the ideal time to start lowering the risk of clinical coronary heart disease, precisely because of the age-related accumulative character of coronary disease risk, is at that time. The age-related accumulative character of coronary disease risk underlines the real place for medicine to attack the problem of coronary heart disease To be sure, *established* clinical coronary heart disease must be treated in any particular patient who already has this disease for he is justifiably primarily concerned about established clinical coronary heart disease. However, more rewarding clinical results can be expected from the treatment of a person *before* he becomes a patient with overt coronary heart disease. In few medical problems does the evidence argue more strikingly in favor of a preventive approach rather than a therapeutic approach to the disease than it does in the case of coronary heart disease This will require a considerable re-orientation in the thinking of the physician and of the public with respect to *who* is a patient. Patients of real importance with respect to clinical coronary heart disease are not patients with established disease but rather the entire adult population of the United States Since there exists no simple way to know without actually making the determinations who the persons are with elevated blood pressures or elevated Atherogenic Index values, or both, and who hence are accumulating coronary heart disease risk at the most rapid rate, it will be essential to consider as patients, or potential patients, every adult in the population

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statistics to confirm these major differences in heart attack frequency for men as compared with women. Every physician is well aware of this difference, and indeed, as mentioned above, some have thought the differences even much larger than those which really exist In the experience of many physicians the occurrence of documentable clinical coronary heart disease in the form, for example, of myocardial infarction in a woman below the age of 40 years is so rare that the initial impression of some physicians is to discount the possibility of this diagnosis except under certain special circumstances Coronary heart disease can and does occur in women even at young ages but it is indeed relatively infrequent as compared with its incidence in men. Where do we go with this type of information? Obviously when a dramatic feature of a disease such as coronary heart disease reveals itself, such as by showing a major sex difference in incidence, there exists the possibility that an understanding of the basis for this sex difference may lead to great clarification in understanding over-all aspects of the disease process itself. In consideration of the male-female difference in coronary heart disease incidence and its possible basis, let us outline the salient features which observational material has provided. These are as follows

1. Early in adult life the incidence of clinical coronary heart disease and fatality therefrom is approximately four or five times in men compared with women.

2 There is a progressive decrease in this ratio of attacks, fatalities, and incidence of clinical coronary heart disease between men and women with advancing years, such that in approximately the eighth decade the incidence rate approaches equality

3 The incidence of hypertension as a factor in the development of clinical coronary heart disease seems to be distinctly more prominent in the female sex than in the male (see Chapter IV).

4 The incidence of diabetes mellitus as a factor in predisposing women to heart attacks seems to be greater than that in men

All of these salient points concerning the differences in coro-

Chapter VIII

THE DIFFERENCE BETWEEN MEN AND WOMEN WITH RESPECT TO CORONARY HEART DISEASE

MEN IN THE United States unquestionably have a higher frequency of manifestations of coronary heart disease, clinical and fatal, then do women. No single fact concerning the occurrence of coronary heart attacks is more striking to the physician viewing this over-all problem. To some extent the difference between men and women with respect to coronary heart disease incidence has been exaggerated in several sources, possibly due to bias in the type of material observed. However, the data available through the United States Vital Statistics concerning the comparative heart attack rates for men and women clearly indicate that at least for relatively youthful groups the frequency of such heart disease in men greatly exceeds that in women, with that difference *shrinking progressively with increasing age*. These data were presented in Table XXIII. Not only do the data presented there indicate that men, on the average, have a greater incidence rate of coronary heart disease than do women at several ages, but certain other tremendously striking features of this difference emerge. Whereas in the age decade from 30-39 years the incidence of fatal clinical coronary heart disease is some 4.5 times in men that which occurs in women, with each passing decade the difference between men and women shrinks so that by the time the seventh decade of life is reached the incidence rate in men is approximately 2 3 times that for the women. That these differences are real for the population in the United States and for the present era is beyond question There is certainly no further proof or evidence required beyond the U. S. Vital

value and that which obtains from the blood pressure value. Therefore it will be necessary to consider not one but both of these factors in determining the risk differences between men and women at various ages

THE BLOOD LIPOPROTEIN (ATHEROGENIC INDEX) FACTOR IN MEN AND WOMEN

Measurements for the S_f0-12, 12-20, 20-100, 100-400 lipoprotein classes and the derived Atherogenic Index values are available for men and women at ages up to 70 years of age. Such information is presented in Table XXVIII for these lipoprotein classes. The Atherogenic Index data are in Table XXIV. Certain facts are clear Whereas the lipoprotein levels are not strikingly different in early life[11], there is a sharp divergence in blood lipoprotein levels between the sexes in the teens and in the twenties, with the males showing higher values of all four important classes of lipoproteins and of the Atherogenic Index than do the females Whereas the males show steep rises in level of the various lipoprotein classes during the third decade of life, the females, on the average, lag behind although there is a slow rise in lipoprotein levels At a somewhat later age when the men are levelling out in average value for the various lipoprotein classes and even showing declining values, the women are showing a marked increase in values, until finally for each lipoprotein class there is reached an age, differing somewhat for the various lipoprotein classes, at which the average level in women becomes equal to the average level in men After that age the average lipoprotein level in women is higher than the average level in men For the Atherogenic Index, which summarizes all the lipoprotein information with respect to coronary heart disease, the age at which the average woman reaches the Atherogenic Index possessed by the average man is 64.5 years Thereafter women show, on the average, higher Atherogenic Index values than do men, at least out to the eighth decade of life. Inspection of the data reveals further that the major differences between the male and the female sex are in the lipoprotein classes of high flotation rate, namely, in the S_f12-20, in the S_f20-100 and

nary heart disease between men and women deserve careful evaluation for whatever leads they may provide with respect to the over-all genesis of coronary heart disease. Possible explanations for these major observations which surround the difference between coronary heart attack rate in men and women fall into two possible categories; (1) The differences observed can be explained on the basis of those factors already known and established to be associated with coronary heart disease, namely the level of certain important lipoprotein classes in the blood (expressed as the composite value, the Atherogenic Index) or the level of the diastolic blood pressure, or both. Or, (2) Certain wholly new and independent factors which have not as yet been evaluated are operative.

The proper approach to this problem scientifically is to determine *first* whether or not either known factor, the lipoprotein levels or the blood pressure, explains the described male-female difference in all its manifestations completely or in part If these major known factors explain the difference *completely*, then there is no reason whatever to go on to the second possibility, namely the search for unknown, untested, unheard of additional factors, since there would be nothing for such factors to explain. Any such search would then be fruitless and a waste of time It is axiomatic in science for this type of problem that, when certain known factors of independent merit associated with a disease exist and when a new observation arises for consideration, one tests whether the new observation is truly new or whether it can be explained by operation of the existing known factors. Any other approach to such a problem is certainly not sound scientific methodology, for it essentially negates the existence of all knowledge already developed. Therefore, the primary step in this evaluation is a determination of whether or not the lipoprotein factor, or the blood pressure factor, or a combination of these two explains any part or all of the difference in male-female incidence of coronary heart disease If such factors do *not* explain the differences observed, it would then be *necessary* to go on to other possible explanations. Total risk of coronary disease arising from established factors is best expressed by multiplication of the risk that obtains from the Atherogenic Index

value and that which obtains from the blood pressure value. Therefore it will be necessary to consider not one but both of these factors in determining the risk differences between men and women at various ages

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TABLE XXVIII

AGE TRENDS FOR THE VARIOUS LIPOPROTEIN CLASSES IN UNITED STATES MALES AND FEMALES*

Lipoprotein Classes

*Age*** (*years*)	*Mean S_f0-12 mg/100ml*		*Mean S_f12-20 mg/100ml*		*Mean S_f20-100 mg/100ml*		*Mean S_f100-400 mg/100ml*	
	Males	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
20	300.0	276.0	30.0	28.0	62.9	41.1	28.0	6.7
25	319.0	293.0	38.7	32.5	73.1	46.9	36.2	9.3
30	338.3	310.5	45.8	31.9	83.0	52.5	41.3	11.8
35	357.0	326.5	51.6	41.1	92.9	58.1	52.4	14.0
40	372.0	338.7	55.1	45.2	101.8	61.3	60.7	16.3
45	381.0	319.6	57.2	48.5	109.1	70.6	67.6	18.9
50	389.0	358.0	57.3	51.3	110.9	77.3	65.6	21.8
55	383.5	361.5	56.2	53.5	103.5	81.3	57.8	21.7
60	373.6	369.2	54.2	55.8	91.3	91.0	50.0	27.3
65	363.5	372.7	52.0	57.9	79.2	97.1	41.8	29.5
70	353.3	375.0	49.7	59.7	68.0	101.9	33.8	31.5

* Recent mean values for lipoprotein levels in women above 30 years, especially of S_f20-400 classes, are lower than earlier published values. The recent values are for employed women at the University of California (Livermore), whereas published values are primarily for women in Framingham. A "best" value is reported here between the two sets. Framingham women have appreciably higher relative weights than do the recently studied employed women.

** Data for lipoprotein levels below 20 years of age are based upon a small series of cases and are hence not reproduced here. See reference 41 for approximate values.

very strikingly in the S_f100-400 lipoproteins. From the lower Atherogenic Index values maintained in the youthful years of adult life by the average woman as compared with the average man and from the fact that the entire distribution of values in women as compared with men is shifted toward lower values, it can be immediately predicted that the heart attack rate should be lower in the female sex during the young adult years than it is in the male sex. The next question to consider is *how much* lower it is predicted to be. In a previous chapter, it was shown that the most consistent explanation of the relationship of coronary heart disease risk with Atherogenic Index and blood pressure require that these factors both operate in an *accumulative* manner rather than as instantaneous factors. Therefore in analysis of this problem concerning the male-female difference in coronary heart disease incidence we may treat the Atherogenic Index values in the male and female on the accumulative basis to determine how much of the excessive risk which characterizes the male sex is thereby explained At 35 years of age the men show a coronary heart disease incidence rate approximately 4.5 times that of women (U S. Vital Statistics). In Chapter VII it was demonstrated, by consideration of successive five year age intervals, that the average 35 year old man has accumulated 1903 units toward his risk of coronary heart disease, that is for the portion of total risk which arises via the Atherogenic Index value. A calculation of the number of units accumulated by the average female during the first thirty-five years of life proceeds along precisely similar lines. For the average female the trends in Atherogenic Index values with age are such that between 30 and 35 years the Atherogenic Index value is 50.4 units, at 25 to 30 years, it is 46.7 units, at 20 to 25 years, it is 42.8 units, at 15 to 20 years, it is 40.7 units, at 10 to 15 years, it is 40.3 units, at 5 to 10 years, it is 40 units, and between 0 and 5 years, it is 40 units Therefore, the total accumulation for the average woman at 35 years of age is expressed in the following, simple algebraic equation,

$$\text{Total accumulation} = 5\times50.4 + 5\times46.7 + 5\times42.8 + 5\times40.7 + 5\times50.3 + 5\times40.0 + 5\times40.0 = 1505 \text{ units}$$

Now to compare the average female with the average male at 35 years in terms of coronary heart disease risk it is necessary

to determine what Atherogenic Index a 35 year old man would have to have if he were to have accumulated 1505 units by 35 years (which is what the above calculation shows that the average woman has accumulated in her first 35 years of life). We may set this required Atherogenic Index value for a 35 year old male at x units and then solve for x. From the trend of Atherogenic Index with age for men, it is known that between 30 and 35 years, such a man would have had an Atherogenic Index value = 96% of x, between 25 and 30 years, 88% of x, between 20 and 25 years, 79% of x, between 15 and 20 years, 73% of x, between 10 and 15 years, 71% of x, between 5 and 10 years, 70% of x, and between 0 to 5 years, 70% of x.

$$\text{The total accumulation} = 5 \times (0.96\,(x)) + 5 \times (0.88\,(x)) + 5 \times (0.79\,(x)) + 5 \times (0.73\,(x)) + 5 \times (0.71\,(x)) + 5 \times (0.70\,(x)) + 5 \times (0.70\,(x))$$

But this total accumulation is being set equal to 1505 units Solving for x yields 54.9 units, which is the Atherogenic Index value a man would have to have at age 35 years to have accumulated as much as has the *average* woman by age 35 years. From Table XV it is now possible to determine how the coronary heart disease risk for this Atherogenic Index value, 54.9 units, compares with the risk for an Atherogenic Index of 69.7 units (which is the average value for men at 35 years. The two relative risks are 2.20 and 3.77 Therefore, with accumulative operation of the Atherogenic Index, the risk tables predict that the average 35 year old man has 3.77 over 2.20, or 1.71 times the cornary heart disease risk of the average 35 year old woman. There is a more refined method for calculating the relative risk of 35 year old men versus 35 year old women, based upon calculation of average risk directly instead of the risk of the person with the average Atherogenic Index value. However such a refined calculation does not materially alter the relative risk for 35 year old men versus 35 year old women obtained above. Thus, Atherogenic Index alone, operating as an accumulative factor, leads to the expectation of a 1.71 fold coronary heart disease risk in men of 35 years as compared with women 35 years of age. But this accounts only for the effect of one of the major known factors determining the risk of coronary heart disease. The other factor, the blood pressure, must be evaluated

before the overall prediction can be compared with observational *data*.

THE CONTRIBUTION OF THE BLOOD PRESSURE EFFECT TO THE DIFFERENCE IN CORONARY HEART DISEASE INCIDENCE BETWEEN MEN AND WOMEN

The contribution of the diastolic blood pressure to the difference in coronary heart disease risk between 35 year old men and women proceeds along lines similar to those for the Atherogenic Index contribution, with the diastolic blood pressure to be considered as an accumulative factor. The average blood pressure trends for men from birth out to late age are available in Table XXV. For the average 35 year old man the diastolic blood pressure is 71.0 mm Hg. The average 35 year old woman has a diastolic blood pressure of 65.3 mm Hg. From the trend of blood pressure with age for the female sex, it can be estimated that between 30 and 35 years this woman had a diastolic pressure of 65.0 mm Hg, between 25 and 30 years, 64.2 mm Hg, between 20 and 25 years, 63.7 mm Hg, between 15 and 20 years, 62.2 mm Hg, between 10 and 15 years, 60.5 mm Hg, between 5 and 10 years, 60.0 mm Hg, between 0 and 5 years, 60.0 mm Hg. Therefore, for this average 35 year old woman the total accumulation toward coronary heart disease risk from diastolic pressure as an accumulative factor = 5x65.0 + 5x64.2 + 5x63.7 + 5x62.2 + 5x60.5 + 5x60.0 + 5x60.0 or = 2178 units. In order to use the Table for relative risk of coronary heart disease versus diastolic pressure (which is based upon data for men) it is necessary now to calculate what diastolic pressure a man would have to have at 35 years if he is to have accumulated as many total units (2178) during 35 years as have been accumulated by the average 35 year old woman. Let x be the value of this required diastolic blood pressure. Then between 30 and 35 years, such a man's pressure would be 0.99 x, between 25 and 30 years, 0.96 x, between 20 and 25 years, 0.94 x, between 15 and 20 years, 0.90 x, between 10 and 15 years, 0.86 x, between 5 and 10 years, 0.85 x, and between 0 and 5 years, 0.84 x. The total accumulation by 35 years of age would be:

$$5(0.99\,x) + 5(0.96\,x) + 5(0.94\,x) + 5(0.90\,x) + 5(0.86\,x) + 5(0.85\,x) + 5(0.84\,x)$$

to determine what Atherogenic Index a 35 year old man would have to have if he were to have accumulated 1505 units by 35 years (which is what the above calculation shows that the average woman has accumulated in her first 35 years of life). We may set this required Atherogenic Index value for a 35 year old male at x units and then solve for x. From the trend of Atherogenic Index with age for men, it is known that between 30 and 35 years, such a man would have had an Atherogenic Index value = 96% of x, between 25 and 30 years, 88% of x, between 20 and 25 years, 79% of x, between 15 and 20 years, 73% of x, between 10 and 15 years, 71% of x, between 5 and 10 years, 70% of x, and between 0 to 5 years, 70% of x.

$$\text{The total accumulation} = 5x(0.96(x)) + 5x(0.88(x)) + 5x(0.79(x)) + 5x(0.73(x)) + 5x(0.71(x)) + 5x(0.70(x)) + 5x(0.70(x))$$

But this total accumulation is being set equal to 1505 units. Solving for x yields 54.9 units, which is the Atherogenic Index value a man would have to have at age 35 years to have accumulated as much as has the *average* woman by age 35 years From Table XV it is now possible to determine how the coronary heart disease risk for this Atherogenic Index value, 54.9 units, compares with the risk for an Atherogenic Index of 69.7 units (which is the average value for men at 35 years. The two relative risks are 2.20 and 3.77. Therefore, with accumulative operation of the Atherogenic Index, the risk tables predict that the average 35 year old man has 3.77 over 2.20, or 1.71 times the cornary heart disease risk of the average 35 year old woman. There is a more refined method for calculating the relative risk of 35 year old men versus 35 year old women, based upon calculation of average risk directly instead of the risk of the person with the average Atherogenic Index value. However such a refined calculation does not materially alter the relative risk for 35 year old men versus 35 year old women obtained above. Thus, Atherogenic Index alone, operating as an accumulative factor, leads to the expectation of a 1.71 fold coronary heart disease risk in men of 35 years as compared with women 35 years of age. But this accounts only for the effect of one of the major known *factors determining the risk of coronary* heart disease. The other factor, the blood pressure, must be evaluated

culated for 45 year olds, for 55 year olds, and for 65 year olds These predictions and their comparison with the observational data from U.S. Vital Statistics are presented in Table XXIX. The agreement based upon the accumulation model can be considered excellent It has been proposed that a difference in the thickness of the intimal lining of the coronary arteries may be a factor helping to account for the male-female difference in coronary heart disease incidence but no real development of any significance has come from this proposal. Another factor proposed concerns the so-called susceptibility of the coronary arteries to the deposition of lipids, the postulation being made that such susceptibility is under the influence of estrogenic hormone. Again this highly speculative proposal has no evidence which appears to substantiate it. Undoubtedly other factors will be and have been proposed At the present time, such factors are speculative and without any distinct evidence to support them.

TABLE XXIX

COMPARISON OF FATAL CORONARY HEART DISEASE INCIDENCE RATE FOR MEN VERSUS WOMEN ESTIMATED FROM ATHEROGENIC INDEX PLUS DIASTOLIC BLOOD PRESSURE WITH OBSERVATIONAL DATA FROM U. S. VITAL STATISTICS

Age Group (years)	*Predicted Ratio of Fatal Coronary Heart Disease (Men/Women)*	*Observed Ratio of Fatal Coronary Heart Disease Rate (Men/Women)*
35	2 10	4 45
45	2 72	3.83
55	2 74	3.20
65	2 62	2.26

THE BASIS FOR THE [illegible] TENSION IN WOMEN [illegible] DISEASE IN COMPA[illegible] CORONA[illegible] DISEASE

In Chapter IV it was pointed out that nearly every reported study in the literature shows elevation in blood pressure to be a more frequent occurrence in the women who develop coronary

But this is to be set equal to the total accumulation for the average *35 year old woman, which is 2178 units.*

Therefore 31.7x = 2178 or x = 68.7 mm Hg, which is the diastolic pressure required at 35 years for the man who has accumulated from diastolic blood pressure as much toward coronary heart disease risk as has the average 35 year old woman. This man is to be compared with the average 35 year old man. For a diastolic pressure of 68.7 mm Hg, the relative risk of coronary heart disease (from Table XIV) is 1.83 x that for the reference value of 50 mm Hg, whereas for a diastolic pressure of 71.0 mm Hg, such relative risk is 2.25 x that for the reference value of 50 mm. *Therefore the average man of 35 years has 2.25 over* 1.83 = 1.23 times the risk of coronary heart disease that a 35 year old man with a diastolic blood pressure of 68.7 mm. However, this latter man was a "calculated" man to provide the same accumulative value from diastolic pressure that characterizes the average 35 year old woman. Therefore diastolic blood pressure alone, operating as an accumulative factor, leads to a prediction that the average 35 year old man should show *1.23 times* the risk of future clinical coronary heart disease that the average 35 year old woman shows.

THE COMBINED EFFECT OF THE DIASTOLIC BLOOD PRESSURE AND ATHEROGENIC INDEX OPERATING *AS ACCUMULATIVE FACTORS IN CORONARY* HEART DISEASE IN MEN AND WOMEN

From the Atherogenic Index alone the relative risk for the *average 35 year old man compared with the average 35* year old woman is 1.71 times as high, and from the blood pressure the relative risk for the man compared with the woman is 1.23 times as high. As developed in Chapter V, the best approximation to *overall risk* of coronary heart disease is obtained by multiplication of the risk from Atherogenic Index by that from diastolic blood pressure. Therefore the overall risk for the 35 year old man is *calculated to be 1.71x1 23, or 2.10 times that for the* average 35 year old woman. By entirely similar methods the predicted coronary disease risk for men versus women may be cal-

The overall coronary heart disease risk was then determined for each person in the usual manner, namely *multiplication* of the risk from Atherogenic Index by that from blood pressure. These overall coronary heart disease risks were then ranked from the highest to the lowest, in separate lists for the men and the women For convenience each group of 100 persons can be subdivided into ten risk categories, each containing ten persons, and the median risk for each category calculated for the ten persons in that category. Such data are presented in Table XXX, ranked from the lowest risk category to the highest for each sex. Now our 100 men and 100 women are each sub-divided into 10 subgroups, for each sub-group the median risk being known and the distribution of blood pressures being known. Suppose now that a very large population sample of 50-59 year old persons were studied during a period when they are overtly healthy. In a person of time of observation de novo clinical coronary heart disease will develop in each of the 10 sub-categories of overall risk, *the number* of cases in each category being directly pro-

TABLE XXX

RANKING OF 50-59 YEAR OLD MEN AND WOMEN UPON MEDIAN CORONARY DISEASE RISK
(10 Categories for Each Sex)

	MEN Median Risk* (setting lowest category = 1.00)	WOMEN Median Risk* (setting lowest category = 1.00)
Lowest Category of 10	1.00	1.00
2nd " "	2.35	1.88
3rd " "	2.77	2.09
4th " "	3.19	2.61
5th " "	4.25	2.94
6th " "	6.25	4.00
7th " "	9.31	4.58
8th " "	13.08	5.85
9th " "	18.65	8.64
Highest " "	50.96	16.94

*Relative risks were calculated from the [illegible]

heart disease at a particular age than in the men who do so. So marked has been this difference in some series that the authors had erroneously concluded that hypertension is not a factor in the development of coronary heart disease in men but is a major factor in its development in women. Hypertension has been conclusively shown to be a major factor in the development of coronary heart disease *both* in men and women. Indeed there exists no reason to believe there is any lack of equivalence of a particular degree of blood pressure elevation with respect to acceleration of sub-clinical coronary heart disease development in men versus women. Why, then, should hypertension be a more frequent finding in women who experience clinical coronary heart disease than in men who develop that disease? Fortunately, there now exists sufficient quantitative information concerning the factors which determine the risk of clinical coronary heart disease in men and women to provide the answer to this highly important question.

From the relationship of coronary heart disease incidence rate with Atherogenic Index and diastolic blood pressure, it should be possible to *calculate* whether or not hypertension should be a *more frequent finding in coronary heart disease among women* than among men. This calculation is, additionally, illustrative of some of the uses of risk data and is presented in detail. A random sample of 100 men and 100 women in the age decade, 50-59 years, from a larger sample of the population study at Framingham, Massachusetts, was selected for this analysis. For each person the Atherogenic Index and the diastolic blood pressure were available. Therefore, for each person the risk of future coronary heart disease can be estimated, utilizing the appropriate risk tables (Table XIV and Table XVI). Before using the risk versus Atherogenic Index table for 50-59 year men to calculate the risks for the women, the equivalent Atherogenic Index for men to accumulate by 55 years the same total number of units accumulated by a woman with a particular Atherogenic Index value had to be determined This was described in detail in Chapter VII. Then both for the 100 men and the 100 women the coronary heart disease risk arising from Atherogenic Index and from diastolic blood pressures were calculated separately.

the lowest risk category. Now for each category the total number of cases, and the number in each category with diastolic pressures above 110 mm Hg are as follows;

Lowest category, 100 total cases, of which 0 have pressures above 110 mm Hg.
2nd category, 188 total cases, of which 0 have pressures above 110 mm Hg
3rd category, 209 total cases, of which 0 have pressures above 110 mm Hg
4th category, 261 total cases, of which 0 have pressures above 110 mm Hg

The total number of de novo cases of coronary disease in women is obtained by adding those in each category, yielding 5053 cases. Of these 953 will be characterized by pressures above 110 mm Hg This represents 18 9% of the total group Therefore, all these calculations lead to the conclusion that 18.9 over 11.2, or *1 7 times* as many women of 50-59 years of age developing coronary heart disease would have shown pre-coronary pressures above 110 mm Hg as would men of 50-59 years of age who develop coronary heart disease. Utilizing a blood pressure of 120 mm Hg, it is calculated that 16 0% of women who develop coronary heart disease would have shown diastolic blood pressures above 120 mm Hg, whereas only 0 4% of men of the same age group who develop coronary disease would have shown pressures above 120 mm Hg. The direction of the effect and the general order of magnitude of the increase in frequency of hypertension in coronary disease in women versus men, predicted from Atherogenic Index-Blood Pressure risk estimates, is therefore in accord with observational experience. Precise estimation of the difference would, of course, be better obtained by the study of much larger population samples Thus, while the very calculation itself takes cognizance of the importance of blood pressure as a risk factor *for both sexes,* the concept still provides consistency with the observational experience that hypertension is a more *frequent* accompaniment of coronary heart disease in women than in men Qualitatively this could have been anticipated from the fact that men and women are more nearly alike up to 55 years of age in blood pressure than in Atherogenic Index. Hence

portional to its risk. Thus, if for the men, we wait until 100 cases of de novo coronary disease arise out of the *lowest category*, the data of Table XXX inform us that, in the same time interval there will be the following number of de novo coronary heart disease cases in the other nine categories:

If lowest category develops 100 cases, then;

2nd category develops	235 cases
3rd category develops	277 cases
4th category develops	319 cases
5th category develops	423 cases
6th category develops	623 cases
7th category develops	931 cases
8th category develops	1,308 cases
9th category develops	1,865 cases
10th category develops	5,096 cases

The total number of cases of de novo coronary heart disease is obtained by adding all the cases together, yielding 11, 177. From the distribution of blood pressure values of the 100 sample men age 50-59 years in each sub-category, the *fraction* of each subcategory with blood pressures above any particular value is immediately known. We may calculate, for example, the number of cases of de novo coronary disease in each sub-category with pressures above 110 mm Hg by multiplying this fraction by the number of cases in the category

Therefore, we can estimate that there will be,

of 100 cases in category 1,	0 above 110 mm Hg
of 235 cases in category 2	0 above 110 mm Hg
of 277 cases in category 3	0 above 110 mm Hg
of 319 cases in category 4,	0 above 110 mm Hg
of 423 cases in category 5,	42 above 110 mm Hg
of 623 cases in category 6,	0 above 110 mm Hg
of 931 cases in category 7,	186 above 110 mm Hg
of 1308 cases in category 8	0 above 110 mm Hg
of 1865 cases in category 9,	0 above 110 mm Hg
of 5096 cases in category 10,	1019 above 110 mm Hg

The total number of de novo coronary disease cases with pressures above 110 mm Hg is 42 + 186 + 1019, or 1247 cases. Therefore, of the 11,177 de novo coronary disease cases in men 11.2% have pressures above 110 mm Hg. Proceeding along similar lines for the women, we can consider a time period long enough for 100 cases of de novo coronary disease to develop in

Chapter IX

THE RELATIONSHIP OF OVERWEIGHT WITH CORONARY HEART DISEASE

In today's medical practice there are few features more associated in the physician's mind with excessive cardiovascular disease in general, and with coronary heart disease in particular, than the phenomenon of overweight. Indeed some physicians have interpreted essentially all the recent dietary work relating to coronary heart disease as being associated with caloric intake and the phenomenon of overweight. While this latter view is incorrect, it does underline the fact that overweight is high in the minds of physicians as a factor predisposing to cardio-vascular disease It is therefore, pertinent to determine precisely to what extent overweight is related to coronary heart disease and then to determine what mechanism may operate to make for an association between overweight and coronary heart disease, assuming such association to exist. This last point is most crucial, for according to current day practice a large number of physicians feel that an overweight patient should reduce in *weight* in the effort to minimize his chances for development of future coronary heart disease. This implies that simply *being* overweight is regarded by the physician as the factor which is responsible for any excessive risk of coronary heart disease. It implies furthermore that there is nothing that can be done to delineate among the overweight individuals those who are especially prone to develop heart disease from those who may have even a lower risk of coronary heart disease than many underweight individuals Therefore, mechanism by which overweight may become associated with coronary heart disease is an issue of paramount importance, once the exact extent of the association is established.

blood pressure would be expected to contribute a greater share of the risk of coronary disease in women than in men, and therefore hypertension should be more prominent in women. The mathematics formalizes this qualitative estimate.

THE ROLE OF ESTROGENIC HORMONES

The large difference in coronary heart disease mortality rate among young women and young men and the finding of markedly lower lipoprotein levels in young women as compared with young men, (a difference which decreases with increasing age) has naturally prompted great interest in the question of whether or not both the difference in disease incidence and in lipoprotein levels might be related to something about estrogenic hormone production in the female compared with the male. The effects of estrogenic hormones upon serum lipoprotein levels have been, and continue to be, extensively studied. Such studies do indeed indicate that pharmacologic estrogenic hormones can profoundly influence serum lipoprotein levels, although they do not provide any evidence concerning physiologic estrogen production or handling as the basis for lipoprotein levels being different in men and women The pharmacologic effects of estrogens upon serum lipoproteins and Atherogenic Index will be discussed in detail in Chapter XV.

The last question concerning differences in coronary heart disease incidence between men and women relates to the findings in diabetes mellitus Since this question is but part of the broader question of coronary heart disease in diabetes mellitus in general, this will be treated in Chapter XII

Chapter IX

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First of all, it must be stated that the association between overweight and coronary heart disease is far from perfect. Every physician who practices medicine realizes fully that many, many patients with coronary heart disease are not overweight, that patients develop coronary heart disease and die from it with weights considered within the normal, or usual, range, and furthermore that many patients develop coronary heart disease and die from it who are underweight by our usual height-weight standards. Such considerations would still be correct even after adjusting for such possibilities as difference in body frame and an incorrect appraisal of the exact amount of true adipose tissue in a particular patient. With all such adjustments it would still be apparent that many people who are underweight or at normal *weights can and do develop coronary heart disease.* Furthermore, even though overweight may be a factor associated with excessive coronary heart disease, many overweight patients remain so for many years without developing any signs and symptoms of coronary heart disease. Where then does the evidence come from which leads to so much emphasis on overweight as a factor in degenerative vascular disease and, in particular, as a factor in the development of coronary heart disease? Probably the single most valid source of evidence on this subject is that which derives from the studies of life insurance policyholders. These studies were in the nature of a follow-up of insured policyholders at varying degrees of overweight and underweight, from those who were markedly overweight to those who were well below the ideal weight for their height and build. Such studies were reported by Dublin[42], the statistician for the Metropolitan Life Insurance Corporation. Individuals were accepted for policies who were overweight, but were rated upward in premium because of their status of overweight. The exact analysis of Dublin's findings relating the coronary heart disease incidence rate in such policyholders to degree of overweight are presented in Table XXXI. It is quite clear from the data presented there that among Dublin's insured policyholders who were 35% overweight the incidence of coronary heart disease was approximately 50% above that in the population of individuals who were at or below ideal weight. This difference is large, it is highly significant,

and is essentially irrefutable. To the author's knowledge no one has published any evidence which would contradict the findings of Dublin on these insured policyholders with respect to the excessive predisposition of appreciably overweight individuals to the development of fatal coronary heart disease. Yet in a variety of ways some investigators have attempted to cast doubt upon this solidly established and highly significant information which has been published by Dublin concerning the relationship of overweight and coronary heart disease. Many who have cast doubt upon this relationship have utilized studies of the extent of overweight in patients with already-established clinical coronary heart disease in comparison with persons free of such manifest disease. For example, Gertler and White[30] in their study of 97 men who developed myocardial infarction below the age of 40 years contrasted with a group of matched controls of the same age but without evidence of myocardial infarction were unimpressed with the difference in the degree of overweight of their myocardial infarction patients and their control series. There is every reason to study the phenomenon of overweight in a series of patients with established clinical coronary heart disease, such as survivors of myocardial infarction, and to contrast the find-

TABLE XXXI

MORTALITY FOR PERSONS RATED UP IN INSURANCE PREMIUMS FOR OVERWEIGHT

(Age group 20-64 years)

(from Dublin)

% Departure from Average Weight (all cases overweight)	*Mortality (Expressed in % of Deaths Relative to Persons of Normal Weight)* MEN %	WOMEN %
Less than 30%	142	139
30-39%	151	148
40-49%	178	156
50-59%	231	175
60-74%	282	145

For all classes of overweight ... that for per...

ings in such a series with those in a series of individuals who have not developed clinical coronary heart disease. In this text analogous data have been presented in previous chapters concerning lipoprotein findings. However, it has been pointed out carefully in previous discussions here that there are some major pitfalls that can deceive the unwary investigator in the use of such clinical material. The crucial issue concerning overweight is the extent to which individuals who are overweight go on to develop clinical coronary heart disease *in the future.* This is essentially the type of study for which Dublin has provided us with information. On the other hand, studies of clinical coronary heart disease already established in the form of survivorship of myocardial infarction are performed on a population of individuals who have not only developed clinical coronary heart disease but *who have been cared for by physicians.* The extremely long history of medical suspicion of the unfavorable aspects of being overweight is such that overweight patients being treated for acute myocardial infarction are almost certain to lose weight during the period of hospitalization for the acute myocardial infarction. Additionally, many of them are encouraged to lose weight and do lose weight during the period of recovery from myocardial infarction. A large number of such individuals will indicate upon questioning that their weight is considerably below *the usual weight that had characterized them during the 5, 10, 15* or 20 years which had preceded their myocardial infarction. On the other hand, many such patients hardly know what their body weight had been before their myocardial infarction. When asked whether they have altered their diet as a result of their myocardial infarction, they will deny that they have, and yet when records are withdrawn detailing previous medical examinations, insurance examinations, or employment examinations, it has been noted repeatedly that their post-myocardial infarction weight is considerably below their pre-myocardial infarction weight. This is not to say that a certain number of patients may not gain weight after myocardial infarction as a result of the lesser physical activity allowed them in the course of their medical advice, but one can be certain that the danger exists, in the study of such clinical material as survivors of myocardial

infarction, of an appreciable loss of weight in many patients. Certainly one should be very wary of accepting data on the body weight of post-myocardial infarction patients as being of real consequence with respect to the average degree of overweight in healthy individuals who will subsequently go on to develop myocardial infarction. Undoubtedly Gertler and White were well aware of the possible biassing which this factor would have introduced into their study. Hence, while it is worthwhile knowing what their findings are, reliance on such evidence to provide us with any evidence of a relationship between overweight and the incidence of myocardial infarction is hardly indicated The same type of criticism should be levelled at a variety of other studies in the literature that have purported to show that the average survivor of myocardial infarction does not show any appreciable degree of overweight in comparison with the average person who has not experienced a myocardial infarction There does exist now in the literature another clear-cut study of the appropriate type concerning the relationship of overweight with development of clinical coronary heart disease, that is, heart disease occurring *after* the determination of the person's *weight status* It is only from such prospective studies of individuals whose weight is known in advance and who are subsequently followed that a valid determination can be made of the extent to which overweight predisposes to clinical coronary heart disease This latter study was conducted by the National Heart Institute of the United States Public Health Service in the community of Framingham, Massachusetts, as part of a long-term survey of the development of cardiovascular disease and other diseases in individuals of a reasonably representative community in the United States These data have been recently published[23]. In that study 52 acceptable, documented cases of "arteriosclerotic heart disease" were observed to develop over a 4 year period out of a population sample of 898 men who had undergone complete physical examinations Analyses of the data showed clearly that the attack rate of coronary heart disease was appreciably and significantly greater during the four-year follow-up period for the overweight men than for otherwise comparable, but not

ings in such a series with those in a series of individuals who have not developed clinical coronary heart disease. In this text analogous data have been presented in previous chapters concerning lipoprotein findings. However, it has been pointed out carefully in previous discussions here that there are some major pitfalls that can deceive the unwary investigator in the use of such clinical material. The crucial issue concerning overweight is the extent to which individuals who are overweight go on to develop clinical coronary heart disease *in the future.* This is essentially the type of study for which Dublin has provided us with information On the other hand, studies of clinical coronary heart disease already established in the form of survivorship of myocardial infarction are performed on a population of individuals who have not only developed clinical coronary heart disease but *who have been cared for by physicians.* The extremely long history of medical suspicion of the unfavorable aspects of being overweight is such that overweight patients being treated for acute myocardial infarction are almost certain to lose weight during the period of hospitalization for the acute myocardial infarction. Additionally, many of them are encouraged to lose weight and do lose weight during the period of recovery from myocardial infarction. A large number of such individuals will indicate upon questioning that their weight is considerably below the usual weight that had characterized them during the 5, 10, 15 or 20 years which had preceded their myocardial infarction On the other hand, many such patients hardly know what their body weight had been before their myocardial infarction. When asked whether they have altered their diet as a result of their myocardial infarction, they will deny that they have, and yet when records are withdrawn detailing previous medical examinations, insurance examinations, or employment examinations, it has been noted repeatedly that their post-myocardial infarction weight is considerably below their pre-myocardial infarction weight. This is not to say that a certain number of patients may not gain weight after myocardial infarction as a result of the lesser physical activity allowed them in the course of their medical advice, but one can be certain that the danger exists, in the study of such clinical material as survivors of myocardial

relationship either of blood lipoproteins or blood pressure with overweight might increase the hazard of overweight persons of developing future clinical coronary heart disease, it would be pertinent to know whether there is or is not there is still left over any extra hazard of coronary heart disease in overweight persons. If there is *no* extra hazard left over to be accounted for, the notion that the phenomenon of overweight per se increases the hazard of coronary disease could be dispelled. If there *is* an extra hazard left over, it is urgent to learn the nature of its possible basis.

OVERWEIGHT, LIPOPROTEIN LEVELS, AND ATHEROGENIC INDEX VALUES

The evidence discussed above clearly implicates overweight as a factor producing an excessive risk of clinical coronary heart disease, and hence, correspondingly, an excessive rate of development of sub-clinical coronary heart disease. The *extent to which* this effect of overweight can be explained by any possible association of overweight with the blood level of the four important lipoprotein classes (S_f0-12, S_f12-20, S_f20-100 and S_f100-400) and with the derived value, the Atherogenic Index, must be understood. Population samples are available for whom the blood lipoproteins, height, and weight have been measured as a routine part of periodic employment examinations so that a reasonable cross section of individuals of both sexes and at various ages is available for study of this issue. The measured values of the various lipoprotein classes and of the combined value which summarizes the information with respect to coronary heart disease, namely the Atherogenic Index, are listed for various degrees of overweight in Table XXXII. In these tabulations degree of overweight or underweight is expressed in terms of the value known as the "relative weight" of an individual. The definition of relative weight, as used here, is the person's actual body weight divided by the "ideal body weight," utilizing the Metropolitan Life Insurance Height and Weight Tables to determine ideal weight. Thus, if an individual is characterized by relative weight of 1.20, it is meant that his weight is 20% above

overweight, men. The actual findings reported by Dawber and co-workers in the Framingham Study were as follows:

Weight Category	Attack Rate of "Arteriosclerotic Heart Disease" in New Cases Per 1000 at Risk (4 year period)
20% or more above median weight	123 cases per 1000
13 to 19% above median weight	105 cases per 1000
0 to 12% above median weight	50 cases per 1000
Below median weight	40 cases per 1000

The evidence derived from this study indicates an association of overweight with heart disease risk of approximately the same order of magnitude as that previously published by Dublin. There existed every reason to expect that these data would confirm Dublin's data, and they do. In the face of such strong evidence from both the study of Dublin on the insured overweights and the data of the Framingham Heart Project there would appear less reason than ever to question the positive relationship of overweight with the subsequent development of clinical coronary heart disease. Rather the strong evidence should make even more suspect conclusions concerning overweight derived from the study of myocardial infarction survivors.

With the clear-cut establishment of an association of overweight with excessive coronary heart disease risk, several questions come to the fore. First, the evidence derived in previous chapters demonstrated two major features characterize individuals in terms of their subsequent risk of clinical coronary heart disease. These are: (1) their blood lipoprotein levels and atherogenic index values, and (2) their habitual blood pressures. It is pertinent, first, to determine the extent to which overweight may influence either of these two factors. For, if either the lipoprotein level and atherogenic index value are elevated on the average in overweight individuals, or if the blood pressure is elevated on the average in overweight individuals, there would exist a well-defined basis for the expectation of a positive association between overweight and the hazard of clinical coronary heart disease. Of even greater importance, some insight into the mechanism by which such association arises would be available. Once an estimate were available of the extent to which a

the ideal weight listed by the Metropolitan Height and Weight Tables No need exists to claim that the "ideal" values listed in the Metropolitan Life Insurance Tables are truly ideal weights. They do serve as a set of useful reference points, and any findings based upon their use would hardly be altered in any significant manner by any other choice of reference weights

All four lipoprotein classes (S_f-12, 12-20, 20-100, and 100-400) and the Atherogenic Index show appreciable rises in average value upon comparison of the significantly underweight individuals with those appreciably overweight, with a fairly smooth rising trend for the intermediary weight groups. Inspection of the table for various individual lipoprotein classes reveals that the effect of overweight is more strikingly associated with elevation of the S_f20-100 and S_f100-400 lipoproteins than it is with elevation of the S_f0-12 and S_f12-20 lipoproteins. At the outset, it must be stressed that these variations in lipoprotein levels and Atherogenic Index values with degree of overweight are *average* findings for the group of individuals in each particular relative weight range In any particular relative weight range, individuals are found who have low, moderate, or even quite high Atherogenic Index values, although there will be a higher frequency of high values of the Atherogenic Index with a higher degree of overweight than with a moderate degree of overweight, and correspondingly a higher frequency of high values with a moderate degree of overweight than for groups markedly below ideal weight Similarly there exists a higher frequency of low values in individuals who are underweight or at ideal weight in comparison with those who are appreciably overweight. These findings all occur because the correlation between relative weight and Atherogenic Index is far from perfect even though it is clear-cut and definite This point is summarized in Table XXXIII, which gives the frequency of various Atherogenic Index values at various degrees of overweight and underweight, in a study group of 834 men in the 30-39 year age category. The entire group of men is then divided into four sub-groups, those 10% or more underweight, those between 10% underweight and 10% overweight, and those 10 to 20% overweight, and those 30% or more overweight (all on the relative weight scale). In each

TABLE XXXII

RELATIONSHIP OF DEGREE OF OVERWEIGHT WITH BLOOD LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(Based upon study of 834 consecutive 30-39 year old men)*

Relative Weight Group	*Number of Cases*	*Mean Lipoprotein Level (mg/100ml)* S_f0-12	S_f12-20	S_f20-100	S_f100-400	*Mean Atherogenic Index (units)*
Less than 0.80 (Mean = 0.76)	11	347.2	56.9	78.6	36.3	61.9
0.80-0.89 (Mean = 0.86)	86	337.8	11.4	70.1	33.2	59.1
0.90-0.99 (Mean = 0.95)	219	319.2	18.2	83.1	38.5	61.6
1.00-1.09 (Mean = 1.05)	219	355.3	51.3	91.6	48.8	69.1
1.10-1.19 (Mean = 1.11)	168	367.1	55.3	100.4	61.1	75.2
1.20-1.29 (Mean = 1.23)	75	360.9	51.9	112.9	78.1	79.1
1.30 or higher (Mean = 1.37)	26	369.2	55.3	116.0	86.7	82.0

* All men were employees at one industrial installation. Examinations were part of periodic medical examinations

coronary heart disease for individuals of several ages at various Atherogenic Index values. Thus, if illustrative considerations are limited to 30-39 year old males, those tabulations will allow a ranking of individuals upon the Atherogenic Index values and a direct calculation of the relative incidence rate of clinical coronary heart disease at one Atherogenic Index value for comparison with the incidence rate at any other Atherogenic Index value. The data of Table XXXII indicate that for 30-39 year old males the individual who is 35% overweight will show an average Atherogenic Index value of approximately 82 units, whereas the individual who is at ideal weight will show an average Atherogenic Index value of 67 units. From Table XV for the value of 82 Atherogenic Index units (in those individuals 35% overweight) the risk of coronary heart disease would be 7.0 times the reference value of 30 A.I. units, and for individuals at ideal weight whose Atherogenic Index value is 67 units, the risk of coronary heart disease would be 3.4 times the reference value. Therefore, the relative risk or rate of mortality from coronary heart disease for these two groups would be the first value divided by the second, or a 7.0 over 3.4 = 2.1 fold increase in attack rate for the overweight group compared with the ideal weight group. The first approximation has been obtained by calculating the risk of coronary heart disease for the average person who is 35% overweight. Therefore Atherogenic Index elevation in overweight persons leads to a prediction of excessive coronary heart disease mortality between the published values of Dublin and of Dawber. However, overall coronary disease risk requires evaluation of the contribution from the blood pressure as well as from the Atherogenic Index.

RELATIONSHIP OF OVERWEIGHT, BLOOD PRESSURE, AND CORONARY HEART DISEASE

The evaluation of a feature such as overweight in relation to excessive coronary heart disease would be incomplete without an analysis of the extent to which overweight may affect blood pressure, and to which this may alter coronary heart disease incidence rate. There have been numerous studies of the relation-

TABLE XXXIII

Distribution of Atherogenic Index Values in the Various Relative Weight Categories

(30-39 year old men)

Relative Weight Category	*Atherogenic Index Values* "Low" Less than 60 (units)	"Moderate" 60-89 (units)	"Elevated" 90-109 (units)	"Markedly Elevated" 110 or higher (units)
Less than 0.90	53.8%	41.2%	1.7%	3.4%
0.90-1.09	38.9%	45.4%	10.6%	5.0%
1.10-1.29	26.0%	51.1%	12.7%	10.2%
Greater than 1.30	26.4%	38.2%	20.6%	14.7%

such category the fraction of the group with markedly elevated, elevated, moderate, and low Atherogenic Index values are presented. It is seen that any value of the Atherogenic Index *can* occur in any of the relative weight categories, but clearly the high values are *more frequent* in the overweight groups than in the other groups. Correspondingly, low Atherogenic Index values *are more frequent in the underweight groups than in the* other weight categories.

EXTENT TO WHICH THE ATHEROGENIC INDEX ELEVATION IN OVERWEIGHT INDIVIDUALS ACCOUNTS FOR THEIR INCREASED CORONARY HEART DISEASE MORTALITY

Dublin's data on insured overweights demonstrated that the 35% overweight individual shows approximately a 1.5-fold mortality from diseases of the coronary arteries compared with the individual who is at ideal weight. Dawber's Framingham data indicate approximately a 3-fold mortality for the same degree of overweight. In the effort to understand the mechanism for this observed increase in mortality, the extent to which the effect of overweight on factors known to be associated with coronary heart disease might be expected to alter the mortality from coronary heart disease must be determined. In Chapter V were presented the tabulations which give the incidence rate for clinical

is given the relative risk (of coronary heart disease or coronary heart disease incidence rate) for various diastolic blood pressure values: For a diastolic pressure of 78.7 mm Hg the coronary heart disease risk is 3.9. For a diastolic pressure of 74.7 mm Hg the coronary heart disease risk is 3.2. Therefore the relative coronary heart disease rate for the average person 35% overweight (whose mean pressure is 78.7 mm Hg) is 1.2 fold that of the average person at ideal weight, (whose mean pressure is 74.7 mm Hg). This is the extent to which the degree of overweight increases coronary heart disease risk via the association of the former with the diastolic blood pressure.

THE COMBINED EFFECT OF ATHEROGENIC INDEX AND BLOOD PRESSURE ELEVATION IN INCREASED RISK OF CORONARY HEART DISEASE IN OVERWEIGHT PERSONS

It was demonstrated earlier (see Chapter V) that the Atherogenic Index and the diastolic blood pressure are independent factors operating to determine the risk of coronary heart disease in any individual. Further, it was shown that the best approximation to the overall risk of coronary heart disease from these two independent factors can be estimated by multiplication of the coronary disease risk factor for the Atherogenic Index effect by that for the diastolic blood pressure. In this case, for the comparison of the average person who is 35% overweight with the average person at ideal weight the Atherogenic Index increases the coronary heart disease risk 2.1 fold, and the diastolic blood pressure increases that risk 1.2 fold. The combined effect of both factors therefore predicts a 2.1x1.2, or 2.5 fold coronary heart disease risk (or incidence rate) for the 35% overweight individual. This lies between the 1.5 fold risk reported by Dublin and the 3 fold risk reported by Dawber. Certainly it would appear that the major effect of overweight in production of an increase in coronary heart disease risk is explainable through the combination of its effects upon the Atherogenic Index and the diastolic blood pressure. There may well exist no excessive risk

*The average of the pressure recorded by the physician (non-reclining) and that taken by the nurse (after 10 minute rest) is used here

ship between overweight and blood pressure[43, 44, 45]. The measured relationship between blood pressure and relative weights for the 30-39 year old men described above is presented in Table XXXIV. The regular progression of increasing average diastolic blood pressure with increasing average degree of overweight is apparent in the data of all investigators. Again, as with the Atherogenic Index, the finding of increase in diastolic blood pressure with increase in weight is an *average* trend. Therefore, at low relative weight, average weight, or at a marked degree of overweight, the diastolic blood pressure can be low, moderate, or high. *But unmistakably there is an increasing frequency of high* values of the diastolic blood pressure with increasing relative weight. From the data of Table XXXIV, the average diastolic blood pressure for 30-39 year old males 35% overweight is 78.7 mm Hg* in contrast with a pressure of 74.7 mm Hg for persons of the same age group who are at ideal weight. In Table XIV

TABLE XXXIV

RELATIONSHIP OF DEGREE OF OVERWEIGHT WITH DIASTOLIC BLOOD PRESSURE

(Based upon study of 834 consecutive 30-39 year old men)

Relative Weight Group	*Number of Cases*	*Mean Diastolic Blood Pressure (mm Hg)* NURSE*	PHYSICIAN**
Less than 0.80 (Mean = 0.76)	11	68.0	75.8
0.80-0.89 (Mean = 0.86)	86	69.1	76.9
0.90-0.99 (Mean = 0.95)	219	70.7	79.2
1.00-1.09 (Mean = 1.05)	249	69.5	79.1
1.10-1.19 (Mean = 1.14)	168	70.2	82.1
1.20-1.29 (Mean = 1.23)	75	71.1	84.6
1.30 or higher (Mean = 1.37)	26	71.8	85.9

* These blood pressures were taken by a nurse after 10 minutes of rest by the subject.
** These pressures were taken by the physician during the course of the physical examination, which preceded the rest period

is given the relative risk (of coronary heart disease or coronary heart disease incidence rate) for various diastolic blood pressure values: For a diastolic pressure of 78.7 mm Hg the coronary heart disease risk is 3.9. For a diastolic pressure of 74.7 mm Hg the coronary heart disease risk is 3.2. Therefore the relative coronary heart disease rate for the average person 35% overweight (whose mean pressure is 78.7 mm Hg) is 1.2 fold that of the average person at ideal weight, (whose mean pressure is 74.7 mm Hg). This is the extent to which the degree of overweight increases coronary heart disease risk via the association of the former with the diastolic blood pressure

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It was demonstrated earlier (see Chapter V) that the Atherogenic Index and the diastolic blood pressure are independent factors operating to determine the risk of coronary heart disease in any individual. Further, it was shown that the best approximation to the overall risk of coronary heart disease from these two independent factors can be estimated by multiplication of the coronary disease risk factor for the Atherogenic Index effect by that for the diastolic blood pressure. In this case, for the comparison of the average person who is 35% overweight with the average person at ideal weight the Atherogenic Index increases the coronary heart disease risk 2.1 fold, and the diastolic blood pressure increases that risk 1.2 fold. The combined effect of both factors therefore predicts a 2.1x1.2, or 2.5 fold coronary heart disease risk (or incidence rate) for the 35% overweight individual This lies between the 1.5 fold risk reported by Dublin and the 3 fold risk reported by Dawber. Certainly it would appear that the major effect of overweight in production of an increase in coronary heart disease risk is explainable through the combination of its effects upon the Atherogenic Index and the diastolic blood pressure. There may well exist no excessive risk

*The average of the pressure recorded by the physician (non-reclining) and that taken by the nurse (after 10 minute rest) is used here.

left over to be accounted for by *overweight per se.* Indeed there never did exist any direct evidence to indicate that load or strain upon the heart due to the phenomenon of overweight *per se* is in any way related to an increased risk of coronary heart disease. The semi-popular "excess baggage" concept of the effect of overweight upon the heart, at least with respect to coronary heart disease, finds no support from these data nor from any other scientific data.

THE PRACTICAL CLINICAL IMPLICATIONS OF THE MECHANISMS BY WHICH OVERWEIGHT INCREASES CORONARY HEART DISEASE RISK

That at least the major share of the effect of overweight in increasing the risk of coronary heart disease operates via the Atherogenic Index and blood pressure effects is hardly a matter of academic importance alone. Clinically, physicians have in general warned the overweight patient that his risk of coronary heart disease is increased by his status of being overweight. In an overall sense this has been completely correct However, now that at least the largest part of the mechanism by which overweight operates to produce an excessive coronary heart disease risk is understood, such a clinical approach is definitely outmoded. For, if an overweight person is one of the many who have "escaped" the effect of overweight upon Atherogenic Index and blood pressure level, then there exists no justification for assignment of an excessive coronary disease risk to that patient Instead such a patient can be re-assured that he does not share the *average* increase in coronary heart disease risk experienced by the overweight group It follows, also, that *some* overweight persons must experience a much greater-than-average effect of overweight upon either the Atherogenic Index or the diastolic blood pressure or both. Such persons are subject to a much greater increase in coronary heart disease risk as a direct result of their being overweight than is the case for the "average" person overweight to the same extent. It becomes apparent, then, that clinically much more can be done to assess the true significance of overweight in a particular patient when the blood

pressure and lipoprotein-Atherogenic Index measurements are available to the physician.

THE EFFECT OF CORRECTION OF OVERWEIGHT UPON ATHEROGENIC INDEX AND BLOOD PRESSURE VALUES

An important question arises in the mind of the clinician whenever a relationship between two physiological or biochemical variables has been demonstrated to exist. That question is, "If one of the variables is changed in a favorable direction, will the other variable also change in a favorable direction?" This is certainly a valid question, for it is possible for two variables to be correlated, and yet to have one such variable uninfluenced when a *change* occurs in the other of the pair. In the present case, the problem centers around whether or not lipoprotein-Atherogenic Index values and blood pressure values will fall if overweight is corrected. It is possible to conceive that some hypothetical third factor controls the degree of overweight and separately controls the Atherogenic Index value. The observed correlation between overweight and Atherogenic Index value could, under these circumstances, be the result of a correlation of both of them with the hypothetical third factor. It can be imagined that correction of overweight might fail to alter the hypothetical third factor and hence fail to alter the Atherogenic Index value. Clearly, such speculation should well be replaced by a direct determination of what happens to lipoprotein-Atherogenic Index values and blood pressure when body weight is altered, both in the direction of an increase and a decrease.

There exist two ways of obtaining direct experimental answers to these questions in human subjects. One method involves the specific experiment of having a group of subjects diet to reduce in weight, with observation serially of Atherogenic Index and blood pressure changes. The other approach involves what may be properly regarded as a "natural experiment," in which individuals are observed over a period of years without any specific medical advice. Of their own choice some will eat more, others the same, and still others, less. Some will increase their physical activity, otheres will not change such activity, and

some will decrease their physical activity. The net result will be that some will increase in weight, others will remain unchanged, and still others will lose weight in such a natural experiment. The changes in a variable, such as Atherogenic Index, can readily be ascertained if such a group of persons is periodically checked as part of a routine examination without any knowledge of the nature of the experiment. Extensive data are now available for both types of experimental approach to the question of the effect of change in weight. Of the two types of data, those derived from the natural experiment are in many ways far more satisfactory to the physician in practise. His real interest lies in knowing what happens to persons altering their weights under the usual circumstances of living. Such natural experiments involve less of the drastic, unphysiologic, and unusual type of dietary regimen, and hence provide information more representative of the dietary patterns persons are likely to adhere to over long periods of time.

The data for such a natural experiment were obtained from serial blood studies of 374 men who were examined on two occasions, one to three years apart, in routine employment medical examinations Weight and lipoprotein levels were determined on both occasions, although none of the persons examined had any idea that such studies were in progress. Therefore it is hardly conceivable that factors such as an effort to lose weight rapidly before a medical visit could have operated to any significant extent in these studies. The subjects were considered on the basis of whether they had lost 5 or more pounds from the first to the second examination, lost 0 to 5 pounds, experienced no change, had gained 0 to 5 pounds, or had gained more than 5 pounds. Lipoproteins of the S_f0-12, 12-20, 20-100 and 100-400 classes plus the derived Atherogenic Index values were measured for all groups of subjects. The average changes for the several groups are presented in Table XXXV. It is clear from those data that the lipoproteins and Atherogenic Index values rise appreciably with increase in weight between the two examinations and that they fall appreciably for those men who decrease in weight between the two examinations This settles definitively the question concerning whether weight alteration does alter lipoproteins

TABLE XXXV

EFFECT OF WEIGHT ALTERATIONS ON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES
("Natural" Experiment Involving 374 Subjects)

	Number of Subjects	Mean S_f0-12	Mean S_f12-20	Mean S_f20-100	Mean S_f100-400	Mean A.I.	Body Weight (pounds)
Persons Losing 5 or More Pounds Between Examinations							
1st Examination	73	351.7	50.6	99.5	61.6	71.9	180.6
2nd Examination	73	336.6	46.8	86.3	11.9	64.6	169.9
Change		− 18.1	− 3.8	− 13.2	− 19.7	− 7.3	− 10.7
Persons Losing 0 to 5 Pounds Between Examinations							
1st Examination	77	369.5	47.9	87.2	56.6	70.0	169.7
2nd Examination	77	358.4	50.7	91.8	53.8	69.7	167.6
Change		− 11.1	∓ 2.6	+ 7.6	− 2.8	− 0.3	− 2.1
Persons Who Did Not Change in Weight Between Examinations							
1st Examination	37	350.3	41.1	81.1	45.1	63.9	163.6
2nd Examination	37	312.6	41.3	81.2	15.6	61.3	163.6
Change		− 7.7	+ 0.2	+ 2.8	+ 0.5	+ 0.4	0
Persons Who Gained 0 to 5 Pounds Between Examinations							
1st Examination	84	315.2	46.3	81.7	43.4	65.2	161.9
2nd Examination	84	352.1	50.0	96.6	60.5	72.1	164.3
Change		+ 6.9	+ 3.7	+ 11.9	+ 17.1	+ 6.9	+ 2.4
Persons Who Gained 5 or More Pounds Between Examinations							
1st Examination	103	355.7	52.2	93.2	49.3	69.5	162.3
2nd Examination	103	360.7	56.2	110.8	68.5	77.6	171.9
Change		+ 5.0	+ 4.0	+ 17.6	+ 19.2	+ 8.1	+ 9.6

some will decrease their physical activity. The net result will be that some will increase in weight, others will remain unchanged, and still others will lose weight in such a natural experiment The changes in a variable, such as Atherogenic Index, can readily be ascertained if such a group of persons is periodically checked as part of a routine examination without any knowledge of the nature of the experiment. Extensive data are now available for both types of experimental approach to the question of the effect of change in weight. Of the two types of data, those derived from the natural experiment are in many ways far more satisfactory to the physician in practise. His real interest lies in knowing what happens to persons altering their weights under the usual circumstances of living. Such natural experiments involve less of the drastic, unphysiologic, and unusual type of dietary regimen, and hence provide information more representative of the dietary patterns persons are likely to adhere to over long periods of time.

The data for such a natural experiment were obtained from serial blood studies of 374 men who were examined on two occasions, one to three years apart, in routine employment medical examinations. Weight and lipoprotein levels were determined on both occasions, although none of the persons examined had any idea that such studies were in progress. Therefore it is hardly conceivable that factors such as an effort to lose weight rapidly before a medical visit could have operated to any significant extent in these studies. The subjects were considered on the basis of whether they had lost 5 or more pounds from the first to the second examination, lost 0 to 5 pounds, experienced no change, had gained 0 to 5 pounds, or had gained more than 5 pounds Lipoproteins of the S_f0-12, 12-20, 20-100 and 100-400 classes plus the derived Atherogenic Index values were measured for all groups of subjects The average changes for the several groups are presented in Table XXXV. It is clear from those data that the lipoproteins and Atherogenic Index values rise appreciably with increase in weight between the two examinations and that they fall appreciably for those men who decrease in weight between the two examinations. This settles definitively the question concerning whether weight alteration does alter lipoproteins

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('Natural' Experiment Involving 374 Subjects)

	Number of Subjects	Mean S_f0-12	Mean S_f12-20	Mean S_f20-100	Mean S_f100-400	Mean A.I.	Body Weight (pounds)
Persons Losing 5 or More Pounds Between Examinations							
1st Examination	73	351.7	50.6	99.5	61.6	71.9	180.6
2nd Examination	73	336.6	46.8	86.3	41.9	61.6	169.9
Change		− 18.1	− 3.8	− 13.2	− 19.7	− 7.3	− 10.7
Persons Losing 0 to 5 Pounds Between Examinations							
1st Examination	77	369.5	47.9	87.2	56.6	70.0	169.7
2nd Examination	77	358.4	50.7	91.8	53.8	69.7	167.6
Change		− 11.1	+ 2.6	+ 7.6	− 2.8	− 0.3	− 2.1
Persons Who Did Not Change in Weight Between Examinations							
1st Examination	37	350.3	41.1	81.1	15.1	63.9	163.6
2nd Examination	37	312.6	41.3	81.2	15.6	61.3	163.6
Change		− 7.7	+ 0.2	+ 2.8	+ 0.5	+ 0.4	0
Persons Who Gained 0 to 5 Pounds Between Examinations							
1st Examination	84	345.2	46.3	81.7	43.1	65.2	161.9
2nd Examination	81	352.1	50.0	96.6	60.5	72.1	164.3
Change		+ 6.9	+ 3.7	+ 11.9	+ 17.1	+ 6.9	+ 2.4
Persons Who Gained 5 or More Pounds Between Examinations							
1st Examination	103	355.7	52.2	93.2	49.3	69.5	162.3
2nd Examination	103	360.7	56.2	110.8	68.5	77.6	171.9
Change		+ 5.0	+ 4.0	+ 17.6	+ 19.2	+ 8.1	+ 9.6

and Atherogenic Index values in the expected direction. The fact that lipoproteins and Atherogenic Index values *are* altered in the expected direction removes any need for a hypothetical third factor which controls body weight and lipoproteins independently. From the clinical point of view, weight reduction can be counted on to reduce lipoprotein-Atherogenic Index values, a favorable trend, whereas weight gain will result in a rise in Atherogenic Index values, a highly unfavorable trend.

The findings from the above-described natural experiment are supported by relatively short term experiments in overweight persons who were induced to lose weight on a prescribed 1000 calorie reduction diet, low in animal fat and in carbohydrate[46]. Twenty-eight women, all significantly overweight, participated in a weight reduction program over a two month period The lipoprotein and Atherogenic Index changes in this study are presented in Table XXXVI. Appreciable falls in all four classes of lipoproteins (S_f0-12, 12-20, 20-100, and 100-400) and in the Atherogenic Index values accompanied the weight loss which averaged 14 pounds for the overall group of 28 women. The probable mechanism by which weight reduction results in lipoprotein lowering, and weight gain, in lipoprotein elevation, are to be discussed in detail in Chapter X. The pertinent issue here is that both in short term medical studies and in long-term natural experiments, weight alterations are paralleled by lipoprotein and Atherogenic Index alterations.

CHANGES IN DIASTOLIC BLOOD PRESSURE WITH CHANGE IN WEIGHT

Precisely the same type of question arises with respect to the relationship of diastolic blood pressure to degree of overweight as arose for the Atherogenic Index-overweight relationship. Will correction of overweight result in a fall in the average diastolic blood pressure? The work of numerous investigators has established satisfactorily[47, 48, 49, 50, 51] that correction of overweight is attended by a fall both in systolic and diastolic blood pressures and that such reductions occur both in originally normotensive and hypertensive persons.

TABLE XXXVI

EFFECT OF SHORT-TERM MEDICAL WEIGHT REDUCTION PROGRAM OF SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(1000 calorie diet in 28 Female subjects)

	S_f0-12 mg/100ml	S_f12-20 mg/100ml	S_f20-100 mg/100ml	S_f100-400 mg/100ml	Atherogenic Index	Body Weight (pounds)
Initial Mean Values	372	93	94	61	81	212
Mean Values after 2 Months on Diet	326	61	72	27	61	198
Changes	− 46	− 32	− 22	− 37	− 20	− 14

EFFECT OF CORRECTION OF OVERWEIGHT UPON CORONARY HEART DISEASE MORTALITY

Both major factors known to be associated with increase in the risk of coronary heart disease mortality, the Atherogenic Index value and the diastolic blood pressure, are positively associated with the degree of overweight. Indeed these two factors together account for essentially all of the known effect of overweight in increasing the incidence rate, or risk, of coronary heart disease. Further, excellent evidence is available that correction of overweight will, on the average, alter the blood pressure factor and the Atherogenic Index in a favorable direction. This would lead to the expectation that correction of overweight should lead to a reduction in the incidence rate, or risk, of coronary heart disease. There already exists cogent, direct evidence to indicate that correction of overweight does, indeed, reduce the risk of fatal coronary heart disease. Dublin and Marks[52], of the Metropolitan Life Insurance Company, have reported on the mortality experience of persons originally rated up in insurance premiums because of overweight but who subsequently received lower ratings after reduction in weight This mortality experience was compared with that for the overall group of persons originally rated up in insurance premium for overweight For their entire group of cases they found for intermediate degrees of overweight a 42% increase in mortality in comparison with persons not rated up in premium, whereas for the group originally rated up but later rerated because of loss of weight the increase in mortality was only 13%. This is a marked reduction in mortality, and it is not even possible to prove that the 13% increase that remained was real For the extreme overweights they found a 79% increase in mortality for the overall group rated up, but for those who were re-rated because of loss in weight the increased mortality was only 9%, which again cannot definitely be proven to be a real increase. Unquestionably this evidence shows that overweight correction does reduce mortality risk. Since coronary heart disease is a major contributor to the excessive mortality observed, it is certain that this particular source of mortality was reduced. Thus not only do all the logical ele-

ments point to the expectation that correction of overweight will reduce the risk of coronary heart disease mortality, but the direct field test provides convincing evidence that this expectation is realized.

Chapter X

DIET AND CORONARY HEART DISEASE

No subject has been more in the limelight of possible approaches to coronary heart disease prevention and treatment than that concerning diet. From numerous sources and from a variety of types of information have come the suggestion that the diet which people habitually consume may in some way be related to their risk of premature coronary heart disease. It will be necessary to consider the validity of evidence concerning possible relationships between diet and coronary heart disease so as to facilitate the physician's decision concerning the practical application of diet in the prevention of coronary heart disease. Prominent among the types of evidence which bear upon this question have been those which associate a high incidence rate of coronary heart disease with prosperity in a country adequate to allow for abundant consumption of certain kinds of foods. Thus the Bantus of South Africa, the Okinawans, the Chinese, and the Japanese (at least during some era) have all been quoted to have a low incidence rate of coronary heart disease, whereas the population of countries of much greater prosperity and a higher food intake, not only of fat but also of calories in general, have been quoted to show a higher incidence rate of coronary heart disease As evidence that deserves careful perusal, such evidence is extremely valuable, for it may provide some major leads toward understanding of coronary heart disease However, among other criticisms, one criticism has been semi-justifiably levelled at such evidence in a serious way. That criticism has essentially stated the following: "If any two of the population groups quoted as having grossly different coronary disease death rates and grossly different diets are compared, it is found that a

wide variety of features can also be used to differentiate these populations beside that of diet."

First, it has been pointed out that the differences in climate and other aspects of the environment for the persons in one country as compared with those for persons in another country are as large, or larger, than the differences in habitual dietary intake of certain foods. Second, there are ethnic differences between the peoples of the various countries involved that might conceivably be associated with alterations as important as, or more important than the difference in food intake. Third, there are gross differences in major occupational activities for the individuals in some of these areas versus those in other areas. Occupation has on other grounds been singled out as a factor involved in the development of coronary heart disease (see Chapter XIV). Fourth, those who feel that stress of living is important have pointed out that various aspects of the complex circumstances of living are such that stresses may be quite different in one geographic area from another. Still other possible differences between persons residing in one area and another could be mentioned over and above any differences in diet that are known to exist To some extent various of these criticisms can be countered and have been countered by investigators interested in epidemiologic investigation For example, the issue of geography, climate and other environmental conditions as being perhaps of more importance than diet is in large measure contradicted by several sets of observations. First, Collumbine[53] has pointed out that the native Ceylonese in Ceylon show a low incidence rate of clinical coronary heart disease and subsist upon a low intake of dietary fat

On the other hand, the Dutch burghers who reside in Ceylon have a much higher incidence of clinical coronary heart disease, an incidence not very different from that which characterizes their cohorts in Holland If it were climatic or geographic conditions per se that were important in lowering the overall rate of coronary heart disease in Ceylon, there would be every reason to expect that the Dutch burghers would show to some extent, at least, the same protection that the Ceylonese are afforded. If the factors of climate and geography were paramount, the Dutch

burghers of Ceylon would be expected to show the same coronary disease attack rate as do the native Ceylonese. That they do not show the same rate is strong evidence that some factor other than geography, *climate, or other aspects of the environment* must be much more crucial in determining the coronary heart disease incidence rate. Similarly, evidence has been adduced by Bronte-Stewart and co-workers[54] that the coronary disease incidence rate in South Africa is much higher for the South African whites than it is for the Bantus in that area. Again, if geography, climatic conditions or similar environmental factors were paramount, it would be anticipated that the whites in South Africa would not fare so much more poorly than the Bantus with respect to the development of clinical coronary heart disease.

Analogous evidence bearing upon this same issue has been developed by others. For example, Larsen[55] has shown that Japanese residing in Western Countries experience a coronary disease incidence rate more nearly comparable with that of whites in such countries than they do with that of Japanese in Japan. If the ethnic factor were of paramount importance, one would anticipate that the Japanese who have migrated to the Western Countries should still show the protection that the ethnic factor *provides, which they apparently do not show This type of evi*dence would counter another of the explanations alternative to diet which have been proposed for the difference in geographic incidence of coronary heart disease.

When all these considerations are weighed pro and con, we are still left with the conclusion that the epidemiologic incidence concerning the relationship of coronary heart disease with the diet is of itself not definitive That it produces valuable clues for direct experimental and clinical investigation is not denied even by those who are most vehemently opposed to acceptance of epidemiologic evidence that habitual diet is a factor in explaining the differences in coronary disease incidence rate in different countries. What is really of concern to the physician dealing with the problem of coronary heart disease in the United States is a knowledge of what role the dietary usually consumed by persons in the United States plays in the development of clin-

ical coronary heart disease. Further, his problem centers about what might be done by dietary means to alter the outlook for the development of coronary heart disease in individuals in this country by dietary alteration. Therefore, what is needed is evidence of a controlled character derived in typical individuals in the United States concerning the effect of dietary factors upon the evolution of clinical coronary heart disease and of the effect of alteration of such dietary factors under the practical circumstances which might be considered feasible in the usual pattern of living There are two major approaches that can be applied scientifically to this question Our interest truly lies in the evolution of serious clinical manifestations of coronary heart disease. Therefore the effect of diet can be studied directly with respect to the rate of development of clinical coronary heart disease. A comparison of diets in large sub-groups of the population could be made with subsequent followup of such sub-groups in the population for an adequate period of time to determine the incidence rate of coronary heart disease in relationship to the type and quantity of the various foodstuffs habitually consumed by the various sub-groups Such studies are by no means simple.

In a country like the United States there exists considerable heterogeneity in the population, heterogeneity in occupational distribution, heterogeneity with respect to climatic and other environmental conditions, and in other respects, all of which would make the question of matching the population sub-groups with respect to variables other than diet a task of major proportions Furthermore, the very task itself of performing a reasonable dietary survey is no small matter, leaving aside the matching upon other variables Up to the present time this type of study has not been accomplished. It is to be hoped that in time such a direct study will be done. One corollary of this type of study would be to alter the diet of a very large sub-segment of the population in a direction considered more favorable with respect to the outlook for coronary heart disease and then to compare the subjects who have altered their diet with a subgroup matched otherwise, but on an unaltered diet, with respect to the incidence rate of clinical coronary heart disease. In many ways such a study might be even more difficult than that of

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each such study is formidable. The experiments involved are laborious, expensive, time-consuming and difficult to execute. Indeed, it is questionable that it is really possible to know the diet of a large series of patients under any circumstances other than institutionalization Thus the type of rigorous proof desired may be outside the realm of practical reality. What, then, should be the position of the physician viewing the evidence concerning a favorable effect of a particular dietary alteration upon lipoprotein or Atherogenic Index values? Should he advise persons concerned with the prevention of clinical coronary heart disease (before or after an initial clinical manifestation) to make such a dietary alteration? There are three major possibilities which are of concern in appraising the prospect that a favorable dietary effect upon lipoprotein levels means a favorable effect upon coronary disease mortality First, it is possible that lipoprotein level elevation and Atherogenic Index elevation may be direct causative factors in coronary heart disease, as much of the evidence suggests strongly that they are. If this be the true nature of the known association of coronary heart disease risk with Atherogenic Index value, then there would be every reason to expect that lowering of the Atherogenic Index value would lower the rate at which new sub-clinical coronary heart disease develops and hence lower the future risk of clinical coronary heart disease.

It is problematical at this time to know the extent to which such alteration in diet might be anticipated to reverse already existing coronary disease Whether such disease can be reversed will need to be determined with direct experimental evidence. However, if the nature of the association is that which has just been considered, there is every reason to anticipate that lowering the levels of the lipoproteins will decrease the rate of development of *new* sub-clinical coronary heart disease. A second possibility is that some third factor, metabolic or otherwise, accounts for the elevation in lipoprotein-Atherogenic Index values and separately accounts for the development of coronary heart disease It is conceivable that dietary alteration can affect the lipoprotein levels favorably but fail to affect this hypothetical third factor In such an event the third factor, still being operative, might allow for the continued high rate of development of sub-

determining the effect of diet in matched population sub-groups without the question of *alteration* of diet.

While the results from such studies would be highly desirable, the many difficulties inherent in the direct approach to measurement of mortality from coronary heart disease in relation to diet or to alteration of diet are quite discouraging. As a result, experimental work upon the relationship of diet to coronary heart disease has taken quite another path, one that is highly favorable since not only does it provide information concerning the effect of diet upon known factors predisposing to coronary heart disease, but also it allows development of some insight into mechanisms by which these factors operate. Thus since the levels of lipoproteins from s_f0 to s_f400 are known to be directly related to the risk of future clinical coronary heart disease, it is entirely logical to determine the effect of any dietary factor or dietary alteration upon the level of all these lipoprotein classes. If increased intake of a particular dietary factor is found to be associated with elevation in level of any of these lipoprotein classes, then a decreased intake of this dietary element can, in general, be anticipated to reduce the level of the particular lipoprotein class and thereby to produce a favorable effect with respect to reduction of coronary heart disease risk. The reader will, of course, state that this represents a subtle transition from a demonstration of a favorable effect upon lipoprotein level to a favorable effect upon the risk of clinical coronary heart disease.

There can be no denial that the final and critical test of efficacy of any preventive or therapeutic measure is a direct test for reduction of *mortality* from coronary heart disease. This would require the study of a large series of cases, subdivided by careful randomization into two sub-groups. In one such subgroup a particular dietary alteration would need to be introduced whereas no such alteration would be made for the other sub-group. Comparison of coronary disease mortality rates at various follow-up intervals thereafter would then be made. This type of direct experiment constitutes the only final and rigorous proof. There is every reason to contemplate such studies of various dietary alterations to obtain the direct and final proof of efficacy. It must also be clear to the physician-reader that

the S_f20-400 and generally also the S_f12-20 lipoproteins. This latter group of patients is, on the average, characterized by a depression in the S_f0-12 lipoproteins. Before considering the specific dietary management of these two lipoprotein disorders, the general results of therapy must be emphasized. In every patient with these disorders where the lipoproteins have been lowered appreciably and maintained lowered (now 15 patients) two signal results have been achieved. First, new xanthomata have failed to develop although the patient had been developing new lesions up to the time the treatment was instituted. Second, old lesions not only did not increase in size but began to decrease in size Many of the old lesions disappeared entirely in a period of several months to two years. Lowering of lipoprotein levels in such patients was achieved in the main by dietary means. Thus, two different types of lipoprotein disorder, each characterized by a development of a lesion extremely similar to the atheroma, show regression of old lesions and inhibition of formation of new lesions when the lipoprotein levels are lowered. From the similarity of the atheroma to the lesions of xanthomatosis it would be a most reasonable and very likely expectation that atheromas would behave similarly when lipoprotein levels are lowered although perhaps at a different rate To be sure, the entire thesis of this book is being developed without the need to consider atheroma formation, since the relationships developed all hold at the clinical level without any dependence upon pathology Nevertheless, since it is probable that the mechanism by which lipoprotein levels and blood pressure come to be associated with clinical coronary heart disease is via their effect on atheroma formation, cognizance of the information concerning patients with xanthomatosis helps strengthen the view that lowering of elevated lipoprotein levels and elevated blood pressures offers great promise for retardation of development of coronary heart disease Other important indirect evidence has been presented in detail concerning the lowered coronary heart disease mortality in insured overweight persons who subsequently reduced in weight (see Chapter IX) In that same discussion it was demonstrated that the average lipoprotein and blood pressure elevations in overweight persons accounts for essentially all the excessive coro-

clinical coronary heart disease even though the dietary alteration had favorably affected the lipoprotein levels. No evidence whatever exists for any such third factor. It is simply being mentioned here as a hypothetical possibility, purely in the realm of speculation, since it would be unscientific to deny its possible existence.

It is strange that therapeutic nihilism in some quarters is so intense that the *possibility* of such a third factor is seized upon as a basis for denying any possible value of dietary reduction of blood lipoprotein levels in altering the rate of development of coronary heart disease. The position of such nihilists is completely unscientific and essentially hopeless to cope with on any rational basis A third possibility must be evaluated with respect to the alteration of lipoprotein levels by dietary means It is conceivable that dietary alteration may affect some hypothetical unproven other factor unfavorably with a net result of either no retardation of coronary heart disease development or even an acceleration of the process Such a possibility cannot be denied on scientific grounds, but the hypothetical noxious effect of diet on some hypothetical factor is at present a wholly undocumented speculative possibility. No facet of the overall picture of this disease suggests the existence of such a factor. Nihilism should not be allowed to retard clinical progress because of the remote possibility of existence of this factor. Were this type of nihilism allowed to operate broadly in medicine, the entire field of pharmaceutical therapeutics would long ago have ceased to exist.

Much indirect evidence argues strongly that reduction in intensity of the predisposing factors will reduce the rate of progression of coronary heart disease One source of such evidence is the study of patients with xanthoma tendinosum or xanthoma tuberosum Such patients exist in the population-at-large because of the fact that on a familial basis they have an enormous derangement of one or another classes of lipoproteins, the same lipoproteins which in the population-at-large are involved in the problem of coronary heart disease. The xanthoma tendinosum patients are characterized by massive elevations of the s_f0-12 lipoproteins and usually also the s_f12-20 lipoproteins, whereas the xanthoma tuberosum patients are characterized by elevation of

(1) The dietary fat intake, both with respect to quantity and type of fat consumed.

(2) The dietary carbohydrate intake.

(3) The dietary calorie intake.

Unfortunately, a great deal of the investigative work that has been done at the clinical level with dietary alteration has suffered from certain major failings. In some studies, multiple dietary variables were being studied at once, rendering interpretation of the results difficult or impossible. For example, patients advised concerning a restriction of the dietary fat intake have in many studies also been advised to restrict the total caloric intake, with the result that weight loss was occurring during the dietary experiment Under such circumstances it is extremely difficult to draw any conclusions concerning the place of dietary fat restriction per se in management, since there existed the uncontrolled variable of marked weight loss. The inverse type of erroneous experiment has also been done Thus in many studies where total caloric intake was restricted, there was a concomitant and essentially inadvertent restriction of fats, carbohydrates and protein Effects upon lipoprotein levels observed during such caloric restriction may very well be the result of restriction of one or more of the specific components of the diet such as fat, protein, or carbohydrate The practical implications of erroneous interpretation of such experiments can be enormous. If an effect truly attributable to fat restriction, for example, is credited to calorie restriction per se its applicability would be considered limited to those situations where calories could be restricted In truth such applicability should have extended to numerous situations where calorie restriction is not feasible but where fat restriction is feasible. In many other dietary studies reported in the literature a variety of pharmacologically potent agents were prescribed at the same time the dietary modifications were made. Dietary data derived from such studies must necessarily be viewed with suspicion until and unless the possibility can be ruled out that the pharmaceutical agents being concurrently administered had no effect upon the biochemical variable under consideration.

Valid evidence concerning specific compositional factors in the diet is best derived from studies in which caloric intake is

nary heart disease in such persons. Furthermore conclusive evidence is available that correction of overweight has in general the effect of reducing elevated lipoprotein levels and elevated blood pressures. Thus it appears inescapable that the most probable basis for the beneficial effect of weight reduction is the lowering of lipoprotein levels and blood pressure. Certain general principles govern any approach to reduction of coronary heart disease risk by manipulation of lipoprotein levels and blood pressure. These principles apply not only to dietary methods but to any proposed pharmacologic approach or to their combination. The real objective of a dietary program would be to affect the combination of lipoprotein and blood pressure factors such that the *net risk* of clinical coronary heart disease will be lowered. Such net risk is the product of that due to the Atherogenic Index multiplied by that due to the blood pressure. Leaving the pressure consideration aside for the moment, coronary disease risk varies with Atherogenic Index. Therefore, should a particular dietary regimen lower the s_f0-12 and s_f12-20 lipoprotein levels but *raise* the s_f20-100 and s_f100-400 lipoprotein levels, the crucial issue would be whether or not the elevation in Atherogenic Index resulting from the rise in s_f20-400 lipoproteins was more than offset by the lowering in Atherogenic Index resulting from the fall in the s_f0-12 and s_f12-20 lipoproteins. This is simply a situation where one must consider whether the regimen does more good than harm If the focus is solely upon which lipoprotein classes fall in level, without consideration of possible rise in other classes, serious errors in medical management can and do result. This is by no means simply a hypothetical possibility Once it is assured that the dietary regimen has a *net* effect of lowering the Atherogenic Index, it is still necessary to insure that it does *not* raise blood pressure significantly, for if it does, the net effect upon coronary heart disease risk might still be unfavorable.

EFFECTS OF DIETARY FACTORS UPON SERUM LIPOPROTEIN LEVELS

Interest in dietary effects upon serum lipoproteins centers largely upon three factors:

content fall in level, e g. s_f0-12, this may cause the total serum cholesterol level *to fall* even though a marked rise has occurred in lipoproteins poor in cholesterol content, e g. s_f20-400. The opposite trend of s_f20-400 lipoproteins from that of s_f0-12 lipoproteins may be of sufficient magnitude to cause a marked rise in Atherogenic Index and hence coronary heart disease risk even though the blood cholesterol level has fallen. Therefore, the most satisfactory data come from those studies which provide information concerning the fate of each lipoprotein class of interest with respect to coronary heart disease under the influence of any particular dietary manipulation.

With respect to dietary fat intake, two separate questions of major interest exist today, with a large body of evidence now having built up concerning each The first concerns the *quantity* of dietary fat consumed and the effect of this upon the several blood lipoproteins of importance for coronary heart disease. The second concerns the type of fat ingested rather than the quantity and the effect of type of fat upon the lipoprotein levels. Two features of dietary fats have been of especial interest; first, whether the fat is of animal or vegetable origin, and second, the degree of saturation of the fat Since amount of fat and type of fat are the issues being considered, evidence must be reviewed for studies where all dietary alterations were made at isocaloric levels, so that weight loss is not involved Where type of fat per se is the issue not only is it necessary that total calories remain constant but also that the total *quantity* of fat consumed daily remains constant. Further in such studies one is especially concerned about relatively long-term effects of diet. Therefore, dietary studies involving relatively few days on any particular regimen are hardly meaningful with respect to the longer term effects of interest, namely whether or not dietary alterations can be made which will produce and maintain lipoprotein alterations of a desirable character over a long period of time. Long term studies were performed during 1950 and 1951 which contrast diets high in fat intake with those low in total fat intake. Nichols and co-workers[46] have reported these carefully controlled studies Diets high in fat of animal origin and those high in fat of vegetable origin have both been contrasted with low fat diets

maintained constant This is especially important since, for obscure reasons, many physicians and lay people alike equate dietary restriction with calorie restriction and are inclined to attribute nearly any effect obtained by dietary means to calorie restriction and weight loss. If dietary manipulation of coronary heart disease risk rested wholly upon calorie restriction and weight loss, a great deal could be done clinically, but of greater importance would be the need for management for the large fraction of the population in whom weight loss and calorie restriction is not feasible but in whom a high coronary heart disease risk still exists. Therefore, careful delineation of which dietary effects depend upon specific food factors and which, upon calorie restriction per se is of intense practical importance.

THE DIETARY FAT INTAKE

Dietary fat has been of interest with respect to coronary heart disease for a very long time, in part because of some of the apparent geographic associations between dietary fat intake, blood lipid levels, and coronary heart disease, early alluded to by Snapper[56] concerning such associations in China. However, many of the earlier studies of the relationship of diet with coronary heart disease via the association of both with blood lipid levels are now primarily of historical interest either (a) because the blood lipid methods utilized were very crude or (b) because the blood lipid measurements then available such as, for example, a serum cholesterol measurement, failed to provide adequate information concerning the fate of each of the important lipoprotein classes with respect to dietary manipulation. A blood lipid measurement which does not adequately reflect what is happening to all the lipoprotein classes between S_f0 and S_f400 can give rise to seriously erroneous impressions concerning the potential efficacy of the dietary alteration. Examples are now well known where a particular dietary manipulation can elevate the level of one band of lipoproteins while depressing the level of other bands. An approximate measure of the lipoprotein levels, such as the serum cholesterol level, reflects only part of the entire change. If certain lipoproteins rich in cholesterol

TABLE XXXVII

Long Term Effects of Diets High in Fat of Animal Origin Versus Diets Low in Total Fat Upon Serum Lipoprotein Levels and Atherogenic Index Values

(Both diets identical in calorie intake)*

Subject	During Diet High in Fat of Animal Origin	During Diet Low in Total Fat	Change
Mean S_f0-12 Lipoprotein Levels (mg/100ml)			
1	394	335	− 59
2	463	333	− 130
3	466	295	− 171
4	341	260	− 81
5	365	273	− 82
Mean for 5 Subjects	405.8	299.2	− 104.6
Mean S_f12-20 Lipoprotein Levels (mg/100ml)			
1	54	56	+ 2
2	100	62	− 38
3	105	63	− 42
4	32	30	− 2
5	63	44	− 21
Mean for 5 Subjects	71.2	51.0	− 20.2
Mean S_f20-100 Lipoprotein Levels (mg/100ml)			
1	126	169	+ 43
2	141	150	+ 9
3	129	132	+ 3
4	40	56	+ 16
5	137	142	+ 5
Mean for 5 Subjects	114.6	129.8	+ 15.2
Mean S_f100-400 Lipoprotein Levels (mg/100ml)			
1	125	308	+ 183
2	100	160	+ 60
3	72	102	+ 30
4	17	33	+ 16
5	56	73	+ 17
Mean for 5 Subjects	74.0	135.2	+ 61.2
Mean Atherogenic Index Values (in units)			
1	93	127	+ 34
2	106	98	− 8
3	100	81	− 19
4	50	47	− 3
5	82	73	− 9
Mean for 5 Subjects	86.1	85.2	− 0.9

* The low fat dietary period is a high-carbohydrate period, since carbohydrate calories replaced those lost from fat

in those studies. The study periods utilized by Nichols for each type of diet were sufficiently long that transitional effects resulting from dietary alteration were minimized. Five male subjects participated in that long-term dietary study, taking all meals at a hospital diet table, save for breakfast which was standard and was eaten at home. *Samples of blood on all five subjects were* drawn once weekly, divided into two aliquots, and analyzed in duplicate to minimize experimental errors. Furthermore, all *dietary periods were of eleven or twelve weeks in duration.* Therefore, the mean levels of lipoproteins for each particular dietary composition reflect no fewer than 22 blood analyses for *each of the subjects studied. Since the overall dietary periods* under consideration include the first week after the person was on the new diet, during which any transitional effects may have existed, the average effects measured for the entire period on a particular diet must actually have been even larger than reported, if the transitional periods are characterized by intermediary lipoprotein values. Therefore all the changes proved to be significant were evaluated in a conservative basis. The diets that were consumed by the individuals during these various periods do not represent formula diets. Instead they were diets prepared in a diet kitchen with kitchen-tested recipes and arranged in menus planned in such a manner that a person could enjoy meals over a long period of time with one or another of these diets What such diets may lack in ultimate chemical precision, they undoubtedly gain in provision of information concerning practical aspects of dieting over long periods under usual, physiologic circumstances of living. The data comparing the long-term lipoprotein levels on a diet high in fat primarily of animal origin and a diet low in fat are presented in Table XXVII. Maintenance of iso-caloricity was achieved by carbohydrate supplementation in the low fat period The regularity of fall in the level of s_f0-12 lipoproteins which occurs with substitution of a diet containing 103 grams of fat per day (93% of which is of animal origin) by a diet containing 18 grams of fat is notable. The s_f12-20 lipoproteins behave in general similarly to the s_f0-12 lipoproteins, falling in level when the high animal fat intake is replaced by a diet low in total fat intake The behavior of

TABLE XXXVIII

LONG TERM EFFECTS OF DIETS HIGH IN FAT OF ANIMAL ORIGIN VERSUS DIETS HIGH IN VEGETABLE OIL UPON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

(Both diets containing same total quantity of fat and calories)

Subject	*During Diet High in Fat of Animal Origin*	*During Diet High in Vegetable Oil*	*Change*
Mean S_f 0 12 Lipoprotein Levels (mg/100ml)			
1	394	290	− 104
2	463	316	− 147
3	466	284	− 182
4	341	269	− 72
5	365	299	− 66
Mean for 5 Subjects	405.8	291.6	− 114.2
Mean S_f 12 20 Lipoprotein Levels (mg/100ml)			
1	54	47	− 7
2	100	70	− 30
3	105	62	− 43
4	32	23	− 9
5	65	53	− 12
Mean for 5 Subjects	71.2	51.0	− 20.2
Mean S_f 20 100 Lipoprotein Levels (mg/100ml)			
1	126	142	+ 16
2	141	127	− 14
3	129	97	− 32
4	40	30	− 10
5	137	147	+ 10
Mean for 5 Subjects	114.6	108.6	− 6.0
Mean S_f 100 400 Lipoprotein Levels (mg/100ml)			
1	125	135	+ 10
2	100	109	+ 9
3	72	60	− 12
4	17	18	+ 1
5	56	61	+ 5
Mean for 5 Subjects	74.0	76.6	+ 2.6
Mean Atherogenic Index Value			
1	93	86	− 7
2	106	85	− 21
3	100	67	− 33
4	50	39	− 11
5	82	76	− 6
Mean for 5 Subjects	86.1	70.6	− 15.5

s_f20-100 and s_f100-400 lipoproteins accompanying this dietary shift was somewhat surprising. Both s_f20-100 and s_f100-400 lipoproteins rose appreciably, though variably among the subjects when the diet high in animal fat was replaced by that low in fat, but with the lost fat calories replaced by carbohydrate. The effect is sufficiently large to be well beyond any question of simply a sampling error, and it has been confirmed repeatedly, both here and elsewhere in the world[57, 58, 59]. There is no question that the low fat, high carbohydrate dietary period is associated with a rise in level of the s_f20-100 and s_f100-400 lipoprotein classes. Two possible explanations of the observed rise is s_f20-100 and s_f100-400 lipoproteins with this dietary shift are: (1) that a fat deficiency might be responsible, or (2) the possibility (which is now known to be correct) that the increase in carbohydrate intake necessary to maintain isocaloricity of the diet is itself responsible for the striking rise in s_f20-100 and s_f100-400 lipoproteins. The conclusion that it is the carbohydrate supplement rather than a possible fat deficiency which is responsible for the rise in s_f20-100 and 100-400 lipoproteins is based upon many sources of evidence to be developed below. First, however, it is important to compare two other dietary periods in this same study of Nichols and co-workers These two periods, again isocaloric, so that weight loss did not occur, both provided the same total quantity of dietary fat but the source and type of fat differed markedly in these two periods. Thus, approximately 100 grams of fat were present in the daily diet of both periods In one case the fat was primarily from animal sources, whereas the fat was primarily from vegetable sources in the other dietary period. In the period of high vegetable fat ingestion it was the liquid, relatively unsaturated cottonseed oil which was utilized The lipoprotein comparisons for these two dietary periods are presented in Table XXVIII It is to be noted from these data that the shift from 100 grams of fat primarily from animal sources to 100 grams of fat primarily in the form of vegetable oil, but with the total caloric intake and fat content of the diet maintained constant, that the s_f0-12 and s_f12-20 lipoprotein levels fell and did so to essentially the same extent as they did when the diet providing 100 grams of fat of animal origin was replaced by a low fat diet.

urated fatty acids in vegetable oil? Second, is the elevation in S_f20-100 and 100-400 lipoproteins observed on the high carbohydrate intake in contrast with the levels observed on both the diet high in animal fat and on that high in vegetable oil due to the increased carbohydrate intake per se or to some type of deficiency in the low fat, high carbohydrate diet?

With respect to the first question, there exists a very important corollary, namely, whether the addition of vegetable oil to a diet *unaltered in animal fat content* can be expected to overcome the noxious lipoprotein-elevating effect of a diet high in fat of animal origin. If vegetable oil provides some hypothetical positively beneficial substance, then it would be anticipated that S_f0-12 and S_f12-20 lipoprotein levels would *rise* when the vegetable oil diet is replaced by a low fat diet, since the hypothetical protective substance would be absent. The direct studies (see Tables XXVII and XXVIII) show that no such *rise* was observed upon shifting from the diet high in vegetable oil to that low in total fat intake. This militates strongly *against* the concept that any beneficial, protective substance exists in vegetable oil which helps to reduce S_f0-12 and S_f12-20 lipoprotein levels. On the other hand, if the animal fat contains a possible noxious substance, the S_f0-12 and S_f12-20 lipoprotein levels would be expected to fall comparably *either* with a replacement of the animal fat by vegetable oil or by a shift from a diet high in animal fat to a diet low in total fat intake. *This is precisely what is observed in carefully controlled studies.* It is reasonable to conclude, therefore, that fat of animal origin contains some factor (or factors) endowed with the noxious capability of elevating S_f0-12 and S_f12-20 lipoprotein levels. Several other investigators throughout the world have in recent years studied the differences between diets high in fat of animal origin and those high in oil of vegetable origin, utilizing the serum cholesterol level as a criterion of effects of various diets upon the blood lipoproteins. As a result of statements in the reports of some of these investigations there is current a notion in some quarters that certain vegetable oils contain a beneficial substance capable of lowering serum cholesterol levels. While the serum cholesterol level is not an adequate guide for blood lipoprotein response, the

Further, the s_f20-100 and *s_f100-400* lipoprotein levels did not rise when vegetable oil was used to replace the animal fat instead of the use of carbohydrate for such replacement. Therefore, a diet which maintains the fat intake constant but which replaces animal fat with vegetable oil is completely like the low fat diet in *one respect,* namely that both diets are characterized by the same degree of lowering of the s_f0-12 and s_f12-20 lipoproteins when contrasted with a diet high in animal fat. The diet high in vegetable oil and the low fat diet (high in carbohydrate), however, *differ* in another very important respect, namely, whereas the s_f20-100 and s_f100-400 lipoprotein levels rise when *carbohydrate is used as the replacement for the animal fat, they* do not rise when vegetable oil is the replacement In summary, the s_f0-12 and s_f12-20 lipoproteins are at the same level on a diet high in vegetable oil or a diet high in carbohydrate, in both of which cases the levels are much lower than on *the diet high in* animal fat The *s_f20-100* and *s_f100-400* lipoproteins are at essentially the same level on a diet high in animal fat or vegetable oil, *in both cases much lower than on a diet high in carbohydrate.* All four classes of lipoproteins are of great importance because of their predictive association with clinical coronary heart disease. Hence, a dietary factor that affects the blood level of any one of them must be carefully weighed in any program designed to alter the risk of coronary heart disease. The remarkable dissociation between the effect of dietary factors on the s_f0-12 and 12-20 lipoproteins from the effect on the s_f20-100 and 100-400 lipoproteins points up the critical necessity of knowledge, for a particular dietary factor, of what it does to all of these lipoprotein classes. Reliance upon any crude measure which fails to discern opposite trends in level for one class of lipoproteins from those for other classes is of real clinical danger

Two fundamental questions of immediate clinical importance present themselves as a result of these findings with respect to diet. First, is the marked elevation in *s_f0-12* and *s_f12-20 lipoprotein levels on a diet high in animal* fat relative either to one high in vegetable oil or to a low fat diet the result of action of some noxious factor in, or attribute of, animal fat or is it a manifestation of a deficiency of some factor such as the unsat-

a rise in the serum level of s_f20-100 and s_f100-400 lipoproteins on a high carbohydrate diet would elevate the blood cholesterol level, provided no fall in the level of other cholesterol-containing lipoproteins obscured this rise. When Ahrens shifted his patient isocalorically from a diet where 70% of the calories were from corn oil to one where only 10% of the calories came from corn oil, he was, in effect, shifting the patient from a very low carbohydrate diet to a very high carbohydrate diet. This increase in carbohydrate intake is itself quite adequate to account for the rise in blood cholesterol levels (via raising s_f20-100 and s_f100-400 lipoprotein levels) he observed without invoking the conclusion he drew that corn oil in large amounts is beneficial. His "positive" effect of corn oil is almost certainly the effect of lowering the carbohydrate intake of the patient.

Beveridge and co-workers[03] did short-term experiments of a somewhat similar nature to those of Ahrens. They showed that the blood cholesterol level fell when a low-fat diet was compared with a usual mixed diet Then when a large fraction of the carbohydrate of the low-fat diet was replaced by corn oil, they observed a further lowering of the serum cholesterol level. This lowering was attributed by Beveridge and co-workers to the beneficial effect of corn oil. No consideration was given by them to the possibility that the lowering of blood cholesterol levels might have been the result of the simultaneous removal of a large amount of the carbohydrate from the diet Since the removal of a great quantity of dietary carbohydrate in the Beveridge experiment would be expected to lower the s_f20-100 and s_f100-400 lipoprotein levels, and hence lower the blood cholesterol level because of the cholesterol content of these lipoproteins, there is no indication whatever for them to have attributed the observed changes to any presumed beneficial effect of corn oil Numerous other studies abound in the medical literature purporting to show a positively beneficial effect of some substance in vegetable oils, but essentially all of them suffer from the oversights described for the specific studies considered here.

At present there exists no valid evidence for the existence of a beneficial factor in vegetable oils or for an "essential" position of the vegetable oils in the human dietary with respect to the phe-

erroneous notions do not arise from this source, but rather from faulty interpretation of the experimental findings. Thus Kinsell[60] replaced animal fats with such vegetable oils as corn oil and observed a lowering of the serum cholesterol level. He drew the conclusion that there must be something positively beneficial about corn oil. Since corn oil contains an appreciable quantity of the unsaturated fatty acid, linoleic acid, he has advanced the idea that such unsaturated fatty acids as linoleic acid are "essential" fatty acids for the human with respect to the control of serum cholesterol levels. Kinsell apparently did not even consider seriously the alternative explanation of a noxious substance in fat of animal origin. Further, his studies were not controlled by the inclusion of a comparison of the high vegetable oil intake with a low-fat intake. Therefore there is no valid reason to consider from his work that linoleic acid is "essential" with respect to the maintenance of low serum cholesterol levels nor to consider that vegetable oils contain any positively beneficial agent capable of effecting a lowering of blood lipoprotein levels

Ahrens and his co-workers[61] studied patients on formula diets, with variation in the type of fat ingested and in the fraction of the total caloric intake provided by fat He reported for one patient that, when the proportion of total calories in the diet was varied upward from 40% to 70% and downward from 40% to 10%, while maintaining protein and total calorie intake constant, there was a rise in blood cholesterol level on the diet with 10% of the calories contributed by corn oil and a prompt *decline* in blood cholesterol level on the diet in which 70% of the calories were contributed by corn oil. He concluded "the reduction in lipid levels may be more pronounced with a high intake of certain specific fats." There is clearly implied in this statement *that a fat such as corn oil provides some specific beneficial agent.* There is no reason to accept this conclusion, from data such as those of Ahrens and co-workers. In the studies of Nichols and co-workers[48] (See Table XXXVII) it was found that a high carbohydrate intake is generally associated with a rise in the serum level of S_f20-100 and S_f100-400 lipoproteins These particular lipoproteins have cholesterol in them to the extent of approximately 13% by weight[62]. Therefore it would be anticipated that

for a decision as to whether dietary cholesterol itself might be the noxious agent involved in diets high in animal fat. Ahrens[85] has presented important evidence that *saturated* vegetable fats behave more like animal fats with respect to effect upon blood lipids when they do like the most unsaturated vegetable oils such as corn oil He suggested that perhaps the saturated fats may themselves be the noxious substances. It is certainly true that animal fats (*excluding* marine animal fats) are, on the average, more highly saturated than are such vegetable fats as unhydrogenated corn oil, cottonseed oil, and safflower oil. Bronte-Stewart and co-workers[86] found that *hydrogenated* groundnut oil produced higher blood cholesterol levels in human subjects than did dietary intake of equivalent amounts of unhydrogenated ground-nut oil However, they also found that the effect of hydrogenated ground-nut oil in raising blood cholesterol levels was slight compared with that produced by the dietary intake of the same *quantity* of fat in the form of egg-yolks.

It appears at present that the natural fats of animal origin such as dairy fat, meat fat, and egg fat have the greatest effect in elevation of s_f0-12 and s_f12-20 lipoprotein levels. Saturated vegetable fats, either those occurring naturally such as coconut oil or those produced by hydrogenation of unsaturated oils, have an adverse effect upon s_f0-12 and s_f12-20 lipoproteins but probably not to the same extent as the animal fats. The unsaturated vegetable oils, while *not beneficial* with respect to lowering of s_f0-12 and s_f12-20 lipoprotein levels, are at least neutral in this regard This latter fact is of itself of tremendous practical consequence, since it allows for the incorporation of vegetable oils into a diet (with attendant increase in palatability and satiety value) that is still adequately restricted in saturated vegetable fas and animal fats to achieve the desirable lowering of elevated s_f0-12 and s_f12-20 lipoprotein levels

DIETARY CARBOHYDRATE INTAKE

The second major problem involved in the effects of diet upon serum lipoprotein levels centers around the elevation of s_f20-100 and s_f100-400 lipoprotein levels during the low fat-

nomenon of control of blood lipid or lipoprotein levels It is clear from all studies that vegetable oils differ from animal fats, with all the evidence pointing to a noxious effect of the fats of animal origin rather than to a beneficial agent in the vegetable oil. The corollary question of whether or not the noxious effect of animal fat can possibly be overcome by *supplementation* of the diet by vegetable oil *without* removal of part or all of the animal fat from the diet comes up repeatedly. The experiments discussed up to this point do not of themselves allow for an answer to this highly pertinent question since they involved the *replacement* of animal fat by vegetable oil. Some poorly controlled studies have been reported in the literature where ostensibly a *supplement* of vegetable oil was provided in the daily diet and where a fall in blood lipid levels was observed. However, review of the protocols of such studies showed that these were actually *replacement* experiments, where either dietary animal fat or carbohydrate or both were *lowered* concurrently with the supposed "supplementation" of the diet by vegetable oil. Since no light is shed upon the problem at hand by such studies they do not merit specific comment here. One carefully performed supplementation study has recently reported by Perkins and Wright[84]. These workers provided a supplement of 50 grams of safflower oil in the diet of 24 subjects for a period of 6 to 7 weeks Safflower oil is very rich in linoleic acid, the fatty acid claimed by Kinsell to be "essential" for lowering of the blood cholesterol level. *No lowering of cholesterol levels could be demonstrated to occur as a result of safflower oil supplementation* in the careful study of Perkins and Wright. It therefore appears necessary to conclude that the noxious effect of animal fat cannot be overcome by provision of a vegetable oil supplement, even when that vegetable oil is one of the richest in its content of linoleic acid.

It is a matter of practical, as well as academic, interest to identify the nature of the noxious agent (or agents) present in fat of animal origin which can effect an elevation of S_f0-12 and S_f12-20 lipoprotein levels In most of the reported studies with dietary animal fat, the diet also provided a reasonably high content of cholesterol *per se*. None of the studies discussed allow

for a decision as to whether dietary cholesterol itself might be the noxious agent involved in diets high in animal fat. Ahrens[65] has presented important evidence that *saturated* vegetable fats behave more like animal fats with respect to effect upon blood lipids when they do like the most unsaturated vegetable oils such as corn oil He suggested that perhaps the saturated fats may themselves be the noxious substances. It is certainly true that animal fats (*excluding* marine animal fats) are, on the average, more highly saturated than are such vegetable fats as unhydrogenated corn oil, cottonseed oil, and safflower oil. Bronte-Stewart and co-workers[66] found that *hydrogenated* groundnut oil produced higher blood cholesterol levels in human subjects than did dietary intake of equivalent amounts of unhydrogenated ground-nut oil However, they also found that the effect of hydrogenated ground-nut oil in raising blood cholesterol levels was slight compared with that produced by the dietary intake of the same *quantity* of fat in the form of egg-yolks.

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DIETARY CARBOHYDRATE INTAKE

The second major problem involved in the effects of diet upon serum lipoprotein levels centers around the elevation of s_f20-100 and s_f100-400 lipoprotein levels during the low fat-

high carbohydrate dietary periods. Is this elevation the result of the high carbohydrate intake or the result of some type of deficiency encountered because of the low fat intake? Data were already present for weight reduction studies (see Chapter IX) which help provide the answer to this question. In those studies a 1000 calorie, low fat, low carbohydrate diet was utilized. If fat deficiency were responsible for an elevation in s_f20-100 and s_f100-400 lipoproteins, it would have been anticipated that the s_f20-100 and s_f100-400 would have become elevated in level during the weight reduction program, *but this did not occur.* Instead the s_f20-100 and s_f100-400 lipoprotein levels *fell* during the weight reduction period. Since the 1000 calorie diet is a low-carbohydrate diet, this is precisely the result that would have been anticipated if these lipoprotein classes are sensitive to the dietary carbohydrate intake, rising with increased carbohydrate intake and falling with decreased carbohydrate intake. The clinical experience of the author, in numerous patients, has consistently confirmed this conclusion, namely that s_f20-100 and s_f100-400 lipoprotein levels are largely controlled by the dietary carbohydrate intake. Indeed the most effective dietary procedure for reducing elevated s_f20-100 and s_f100-400 lipoprotein levels is the reduction in the patient's habitual dietary carbohydrate intake.

The mechanism by which carbohydrate excess in the diet produces elevation of s_f20-100 and s_f100-400 lipoprotein levels remains unexplained at this time. Two possible explanations currently under consideration are that (a) dietary carbohydrate in abundance spares the utilization of fat from s_f20-100 and s_f100-400 lipoproteins from the blood for energy purposes and hence results in an increase in their levels or (b) that the conversion of dietary carbohydrate to fat either for storage or utilization involves a transport phase during which the s_f20-100 and s_f100-400 lipoprotein levels are elevated. Whatever be the precise biochemical mechanism, the practical implications of the carbohydrate effect for the prevention and treatment of clinical coronary heart disease are extensive.

THE CALORIE INTAKE

Thus far consideration has been given to the dietary intake of fat, both with respect to quantity and origin, and the dietary intake of carbohydrate. All of the studies which show the effects of alteration of these dietary factors have been done at isocaloric levels, with the subjects neither gaining nor losing weight. Hence, calories were not involved as a variable. It cannot be overemphasized that, *without* alteration of weight or calorie intake, blood lipoproteins can be altered by certain dietary shifts. However, the lipoprotein alterations which occur when calorie intake and weight are altered are of much interest. The changes in blood lipoproteins both in experimental alteration of weight and in the "natural" experiment where individuals gain or lose weight over a long period of time are presented in Chapter IX in the general discussion of overweight, correction of overweight, and their relationship to lipoprotein levels Associated with a correction of overweight by calorie restriction there occurs a fall in blood level in all the major classes of lipoproteins, s_f-12, 12-20, 20-100 and 100-400 In the light of the immediately previous discussion, the probable explanation for the fall in lipoproteins which is observed when an individual who is overweight goes on a calorie restricted diet can be evaluated A person who is habitually eating more calories than he needs to maintain an ideal weight is taking in too many calories either in the form of protein, of fat, or of carbohydrate or of some combination of these Of these three, it is most likely that any real excess in calories is coming in the form of an excess of fat and/or carbohydrate as a result of the types of habitual diets generally consumed by Americans Of the excess fat which would be consumed, undoubtedly a fair share would be of the relatively saturated varieties, either animal fat or hydrogenated vegetable fat. This being the case such a person might be anticipated to show, in general, some elevation in the s_f0-12 and 12-20 levels as a result of his habitual excessive fat intake, or some elevation in the s_f20-100 and 100-400 levels as a result of a habitual excess carbohydrate intake, or both Therefore, when such a person goes on a calorically restricted diet in the effort to correct over-

high carbohydrate dietary periods. Is this elevation the result of the high carbohydrate intake or the result of some type of deficiency encountered because of the low fat intake? Data were already present for weight reduction studies (see Chapter IX) which help provide the answer to this question. In those studies a 1000 calorie, low fat, low carbohydrate diet was utilized If fat deficiency were responsible for an elevation in s_f*20-100* and s_f*100-400* lipoproteins, it would have been anticipated that the s_f*20-100* and s_f*100-400* would have become elevated in level during the weight reduction program, *but this did not occur. Instead the* s_f*20-100 and* s_f*100-400 lipoprotein levels fell during* the weight reduction period. Since the 1000 calorie diet is a low-carbohydrate diet, this is precisely the result that would have been anticipated if these lipoprotein classes are sensitive to the dietary carbohydrate intake, rising with increased carbohydrate intake and falling with decreased carbohydrate intake. The clinical experience of the author, in numerous patients, has consistently confirmed this conclusion, namely that s_f*20-100* and s_f*100-400* lipoprotein levels are largely controlled by the dietary carbohydrate intake. Indeed the most effective dietary procedure for reducing elevated s_f*20-100* and s_f*100-400* lipoprotein levels is the reduction in the patient's habitual dietary carbohydrate intake

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saturated vegetable fat can be replaced by any of a variety of vegetable oils such as cottonseed oil, corn oil, safflower oil, sunflower oil, soya oil, or peanut oil, without fear of producing a rise in lipoproteins through addition of these vegetable oils. In other words, the vegetable oils of these type are essentially without any effect, favorable or unfavorable. However the absence of any adverse or beneficial effect is in itself a highly beneficial feature, since this means that the diet that is possible for such an individual produces no real loss in palatability, satiety value, and enjoyment relative to that which utilizes the animal fats. Such a diet is much more readily accepted and enjoyed by a patient than would be a low fat diet. If the patient with elevated s_f0-12, or s_f0-20 lipoprotein levels is not overweight, he can ill afford to lose any of his dietary calories by simple removal of the animal or saturated fat from his diet. He needs replacement of calories to avoid weight loss. But loss of weight has been shown above *not* to be an essential part of this problem of lowering the s_f0-12 or s_f0-20 lipoproteins. It is rather a question of the type of dietary fat consumed Therefore, even though such an individual maintains his calories by replacement with one of the vegetable oils and thereby maintains his weight, he will generally experience a favorable reduction in lipoprotein levels. On the *other hand*, if such a patient is overweight, there would be every reason to attempt to reduce some of the calories in his diet and in this attempt to concentrate upon those calories deriving from saturated vegetable fat or animal fat, since they are for him the offenders involved in maintaining high s_f0-12 and 12-20 levels.

There exist many persons who are characterized by low levels of the s_f0-12 and 12-20 lipoproteins, but who demonstrate very high levels of s_f20-100 of s_f100-400 lipoproteins or both The elevation in these classes of lipoproteins is sufficient in many such patients to produce markedly *elevated* Atherogenic Index values and, hence, high coronary heart disease risks in spite of their low levels of the s_f0-12 and 12-20 lipoproteins In this type of patient efforts to decrease the coronary heart disease risk through the advocacy of a low fat diet or of a *replacement* of animal fat with vegetable oil will be to no avail in the vast majority of cases, for the lipoproteins that are elevated in these persons are *not*

weight and when he reduces some of the animal fat (or saturated fat intake) in his diet as well as some of the carbohydrate intake in his diet, it is not surprising that we should see an average trend downward of the four classes of lipoproteins. During calorie restriction dietary alterations are being made which are *known* to affect either one group of lipoproteins or another, or both. Whether or not any factor beyond the reduced animal fat intake or the reduced carbohydrate intake or both is responsible for the fall in lipoproteins which occurs when an individual restricts dietary calories and loses weight cannot be stated. However, there exists no positive evidence that any such effect operates over and above that which can be explained by the animal fat restriction and/or the carbohydrate restriction in such a low calorie diet. The overweight individual who is taking in too much animal, or saturated, fat and too much carbohydrate habitually has of course the best opportunity to reduce lipoprotein levels since he can to good advantage lower two types of substances in the diet which are known to have unfavorable influences upon the blood lipoproteins, the Atherogenic Index, and the coronary heart disease risk.

THE PRACTICAL CLINICAL APPLICATIONS OF THE DIETARY FINDINGS

It is evident that no single dietary regimen can be prescribed that will cover all the types of situations encountered with respect to blood lipoprotein distribution in the effort to reduce clinical coronary heart disease risk. Thus there are individuals who carry an excessive risk of coronary heart disease almost wholly because of a marked elevation of the S_f0-12 and 12-20 lipoproteins, and who show either usual or lower-than-usual levels of the S_f20-100 and 100-400 lipoproteins. For this type of individual there is excellent reason to prescribe a trial of a diet restricted in fat of animal origin or saturated fat of vegetable sources. In many such individuals the lipoproteins of the S_f0-20 class will fall markedly, there will be a corresponding improvement in the Atherogenic Index, and the patient may be expected to benefit. The calories lost from the animal fat or

saturated vegetable fat can be replaced by any of a variety of vegetable oils such as cottonseed oil, corn oil, safflower oil, sunflower oil, soya oil, or peanut oil, without fear of producing a rise in lipoproteins through addition of these vegetable oils. In other words, the vegetable oils of these type are essentially without any effect, favorable or unfavorable. However the absence of any adverse or beneficial effect is in itself a highly beneficial feature, since this means that the diet that is possible for such an individual produces no real loss in palatability, satiety value, and enjoyment relative to that which utilizes the animal fats. Such a diet is much more readily accepted and enjoyed by a patient than would be a low fat diet. If the patient with elevated s_f0-12, or s_f0-20 lipoprotein levels is not overweight, he can ill afford to lose any of his dietary calories by simple removal of the animal or saturated fat from his diet. He needs replacement of calories to avoid weight loss But loss of weight has been shown above not to be an essential part of this problem of lowering the s_f0-12 or s_f0-20 lipoproteins. It is rather a question of the type of dietary fat consumed Therefore, even though such an individual maintains his calories by replacement with one of the vegetable oils and thereby maintains his weight, he will generally experience a favorable reduction in lipoprotein levels. On the other hand, if such a patient *is* overweight, there would be every reason to attempt to reduce some of the calories in his diet and in this attempt to concentrate upon those calories deriving from saturated vegetable fat or animal fat, since they are for him the offenders involved in maintaining high s_f0-12 and 12-20 levels.

There exist many persons who are characterized by low levels of the *s_f0-12 and 12-20 lipoproteins*, but who demonstrate very high levels of *s_f20-100 of s_f100-400* lipoproteins or both. The elevation in these classes of lipoproteins is sufficient in many such patients to produce markedly elevated Atherogenic Index values and, hence, high coronary heart disease risks in spite of their low levels of the s_f0-12 and 12-20 lipoproteins. In this type of patient efforts to decrease the coronary heart disease risk through the advocacy of a low fat *diet or* of a replacement of animal fat with vegetable oil will be to no avail in the vast majority of cases, for the lipoproteins that are elevated in these persons are not

sensitive to the composition or quantity of fat in the diet. Rather, they are very sensitive to the quantity of carbohydrate in the diet. *Therefore, in clinical practice, such patients should be treated* with a diet restricted in carbohydrate. Here again, vegetable oils represent a very useful agent in the diet, for the calories that are lost from carbohydrate can be supplanted by those from vegetable oils with excellent palatability of the diet. This is expecially important in the patient who is already at ideal weight or is underweight and cannot afford to lose such calories For the patient with high s_f20-100 and 100-400 lipoprotein levels who is overweight and who can and should lose some of the calories, his caloric restriction and the correction of his overweight can be made more *meaningful* if such caloric restriction is focussed on the carbohydrate intake.

Lastly, physicians will encounter patients who have what may be called "across the board" elevations of all four important classes of lipoproteins These patients require a still different *dietary approach. If the patient is overweight some of the cal*ories which are in excess should be deleted from the diet both in the form of animal fat and of carbohydrate. In this situation the calories lost require no replacement. If such a patient is not overweight, then the appropriate diet still would require reduction of the intake of animal fat (or saturated vegetable fats) on the one hand, *and* of carbohydrate on the other. This means that supplementation of the calories required to maintain weight would have to come from vegetable oils. If attention is paid only to one class of lipoproteins, full advantage of the dietary approach is hardly being taken for the particular patient, and in certain instances serious errors of management can eventuate. For example, if a patient has an elevation of s_f20-100 and 100-400 lipoproteins (the carbohydrate-sensitive group), and if the physician, failing to realize the indication for a low-carbohydrate diet, prescribes a low fat diet for this patient, he will fail to accomplish his objective because he is not changing any dietary factor that can be expected to influence those lipoproteins of importance in such a patient. Secondly, he may do some real harm because of the fact that many patients who restrict fat in their diets replace the fat freely with carbohydrate. In this particular

type of patient, sensitive to carbohydrate, the additional carbohydrate can be regarded as an insult which will raise s_f20-100 and s_f100-400 lipoprotein levels still further. There are many patients, however, who can replace *some* of their animal fat with carbohydrate in the effort to lower their s_f0-20 lipoproteins by animal fat (or saturated fat) restriction because they are not very sensitive to the carbohydrate effect and will not experience any appreciable rise in s_f20-100 and 100-400 lipoproteins. This can only be determined by direct trial in each particular patient. However, it is through the careful assessment both of the s_f0-20 and the s_f20-400 lipoproteins that one can, with certainty rather than with guesswork, determine whether a particular dietary regimen is influencing a patient in a favorable direction. The lipoprotein measurements can aid the physician to appreciate whether further dietary changes are still indicated, including the type of dietary changes indicated to try to achieve desired results.

The irrational, blanket use of a particular dietary regimen in all persons irrespective of lipoprotein distribution is not to be condoned Such generalizations as "we all eat too much fat," or "we all eat too much animal fat" merely reflect a lack of understanding of major progress *in the* understanding of dietary factors in relation to risk of coronary heart disease. *There is of* course some element of truth in such generalizations, but there is also a considerable element of falsehood in *them*. For a large segment of the population the statement that "we eat too much carbohydrate" is much closer to reality Action based upon uncritical generalizations may do almost as *much medical* harm as good, and in individual cases we can be certain that more harm than good will result It can be regarded as fortunate that enough knowledge is now available for a critical approach to dietary management and such knowledge should be fully utilized by the practising physician

Chapter XI

CIGARETTE SMOKING AND CORONARY HEART DISEASE

It is commonplace in medical practise to find that physicians advise patients with clinically-manifest coronary heart disease to cut down on smoking, especially those individuals with a history of heavy cigarette smoking. Evidently, the impression has been widespread medically that in some way cigarette smoking is unfavorable for the patient with clinically documented coronary heart disease. Some of this advice is based upon the suspicion that tobacco may produce coronary artery vasoconstriction, which, in the face of an already embarrassed coronary blood flow, is regarded as highly unfavorable. All this pertains to the person with already-established clinical coronary heart disease. Of even greater importance is the question of whether or not cigarette smoking is associated with any increased risk of *future* clinical coronary heart disease in the vast bulk of the population-at-large in overt health. This question might be put another way, "Does cigarette smoking accelerate the rate of development of *subclinical* coronary heart disease?" On this question general medical opinion has for long been divided, largely, of course, because sound evidence upon which a meaningful answer could be based simply was unavailable. Several significant avenues of approach may be contemplated in the effort to answer this question. Information is now available from scientific observation not only to answer the question in the affirmative, namely that cigarette smoking is associated with acceleration of the rate of development of subclinical coronary heart disease, but also to understand the probable mechanisms through which the effect is mediated.

RETROSPECTIVE EVIDENCE CONCERNING CIGARETTE SMOKING

The study of smoking histories in persons who have survived a clinical manifestation of coronary heart disease and in persons otherwise matched (by age, sex, etc.), but without clinical coronary heart disease has been performed by Gertler and White[36] and by Yater and co-workers[22]. The Gertler and White study was done on their series of 97 men who had had a myocardial infarction below the age of 40 years and who had survived the episode. A matched control group of men was also questioned by these workers with reference to smoking habits. While it was found that both the myocardial infarction survivors and the men of the matched control group had appreciable numbers of cigarette smokers amongst them, two facts became evident as a result of the questioning concerning cigarette-smoking habits:

(1) The average number of cigarettes habitually smoked by the group of myocardial infarction survivors was approximately 50% higher than the average number of cigarettes habitually smoked per day by the matched control group.

(2) There were approximately twice as many non-smokers among the matched control men as there were in the group of survivors of myocardial infarction.

Yater and co-workers did a similar retrospective study in a series of men between 18 and 39 years of age who experienced a non-fatal [illegible]
Th[illegible]
gro[illegible] a matched control Army group of men. They found that amongst the myocardial infarction group 53% reported having smoked five or more cigarettes per day and for the matched control group 57% reported having smoked five or more cigarettes per day However, a very striking difference was found when the groups were considered on the basis of having smoked ten or more cigarettes per day. There were 68% of the myocardial infarction group who reported smoking this much, whereas only 19% of the matched control group who reported smoking ten or more cigarettes per day.

The studies of Gertler and White and of Yater and co-workers are quite consistent with each other, both indicating

that heavy cigarette smoking was distinctly more frequent among the myocardial infarction cases than among their matched controls. Within the limitations of this type of study involving retrospective questioning, there appears, from the evidence, to exist an association between heavy cigarette smoking and subsequent coronary heart disease. There are, however, good reasons why such evidence by itself can be regarded as inadequate to establish the relationship between cigarette smoking and coronary heart disease. First, there is the possibility that the answers given by the myocardial infarction patients may, in part, have been influenced by their own suspicion that cigarette smoking had in some way contributed to their development of coronary heart disease. Under such circumstances there would have existed a tendency for this group to overestimate the average number of cigarettes smoked. Furthermore, since such evidence arises primarily from the study of *survivors* of myocardial infarction, there are missing from the series those persons who had not survived their myocardial infarction and who therefore were unable to provide answers concerning their smoking habits. The possible influence of this deletion is difficult to assess

Thus, the retrospective evidence, while highly suggestive of an association between cigarette smoking and later clinical coronary heart disease, is inconclusive A far more satisfactory approach is found in the *prospective* type of study, where a determination is made of the smoking habits of a large number of persons, preferably tens or hundreds of thousands, at a time when they are overtly in health and free of evidence of clinical coronary heart disease. Out of such a large series of persons in overt health there will, with the passage of time, grow a number of cases of *de novo* clinical coronary heart disease, some surviving, others not For *these* cases of clinical coronary heart disease the smoking history will have been known *in advance* of the clinical occurrence of coronary heart disease. Such smoking histories can neither be influenced by survivorship from the clinical episode nor by any preconceived notions of the subjects with respect to the possible relationship of cigarette smoking with coronary heart disease. In such a study the time required for a definitive answer is largely dependent upon the number of per-

sons in the original large group under observation. The larger the number of persons in overt health who are questioned concerning smoking habits, the sooner will there be a sufficient number of episodes of clinical coronary heart disease so that an analysis can be made of possible relationships between cigarette smoking and the risk of clinical coronary heart disease. Fortunately such a study has now been done on a very large scale by Hammond and Horn[67] of the American Cancer Society, with highly conclusive results.

In the American Cancer Society study field workers interviewed over 200,000 persons with respect to their smoking habits, that is, whether they had ever smoked, if yes, how much did they smoke and what (cigarettes, cigars, or pipes), and whether or not they quit smoking These findings were maintained on file and during the ensuing months and years a number of clinical episodes of coronary heart disease occurred in this very large population sample under study. The early findings from this study were published by Hammond and Horn in 1954[67]. The results showed clearly that men in their fifties and sixties who were regular smokers of cigarettes developed approximately 1½ to 2 times as many myocardial infarctions per thousand men per year as did those men who had never smoked cigarettes. Such evidence, derived by the questioning of a large sample of the population *first* and then observing *thereafter* who develops clinical coronary heart disease is free of all the criticisms that may be levelled at studies involving the questioning of men who have survived one or more episodes of clinical coronary heart disease. The Cancer Society evidence hardly leaves room for doubt or question concerning the existence of a positive association between heavy cigarette smoking and an excessive incidence rate of clinical manifestations of coronary heart disease. Yet consistently in certain quarters there has existed an intensive effort to belittle the significance of the highly important findings of Hammond and Horn.

One common statement concerning these studies is that the proof of a higher incidence rate of clinical coronary heart disease in regular cigarette smokers than in non-smokers does not *of itself* prove that cigarette smoking is a *cause* of clinical coronary

that heavy cigarette smoking was distinctly more frequent among the myocardial infarction cases than among their matched controls. Within the limitations of this type of study involving retrospective questioning, there appears, from the evidence, to exist an association between heavy cigarette smoking and subsequent coronary heart disease. There are, however, good reasons why such evidence by itself can be regarded as inadequate to establish the relationship between cigarette smoking and coronary heart disease. First, there is the possibility that the answers given by the myocardial infarction patients may, in part, have been influenced by their own suspicion that cigarette smoking had *in some way contributed to their development of coronary* heart disease. Under such circumstances there would have existed a tendency for this group to overestimate the average number of cigarettes smoked. Furthermore, since such evidence arises primarily from the study of *survivors* of myocardial infarction, there are missing from the series those persons who had not survived their myocardial infarction and who therefore were unable to provide answers concerning their smoking habits The possible influence of this deletion is difficult to assess

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THE BASIS FOR THE OBSERVED ASSOCIATION OF CIGARETTE SMOKING AND CORONARY HEART DISEASE

With the solidly-established finding that cigarette smoking *is* positively associated with excessive coronary heart disease, the prime question arises as to whether new, or independent, information is provided. Either cigarette smoking becomes associated with excessive coronary heart disease via a relationship of cigarette smoking with one of the already established factors in coronary disease development, or via some wholly new mechanism. The only factors that still stand critical testing for provision of *independent* information about the risk of an individual's developing clinical coronary heart disease are:

(1) The blood level of the S_f0-12, 12-20, 20-100, and 100-400 lipoproteins.

(2) The diastolic blood pressure.

It is therefore necessary to know whether cigarette smoking is or is not related to the level of any of these blood lipoproteins and whether or not it is related to the level of the diastolic blood presure If *no* such relationships exist, then it would follow that cigarette smoking must be *independently* related to the development of clinical coronary heart disease and that the smoking history of an individual provides *additional* information concerning his risk of future clinical coronary heart disease. If, on the other hand, demonstrable relationships exist between cigarette smoking and the blood lipoprotein levels, or between cigarette smoking and the diastolic blood pressure, or both, it becomes necessary to determine whether such relationships account for part or all of the observed relationship between cigarette smoking and the incidence rate of clinical coronary heart disease

CIGARETTE SMOKING AND BLOOD LIPOPROTEIN LEVELS

Direct experimental data are now available for a large scale study of humans which provide the extent of relationship of cigarette smoking with lipoprotein levels and atherogenic index values The results were originally reported on 461 persons[69],

heart disease. The reasoning behind such criticism is that possibly a certain type of individual is prone to develop clinical coronary heart disease and is (for reasons not given by the critics) the type of person who is likely to become a regular smoker of cigarettes. If this be true, it is argued, the proneness to coronary heart disease might still exist even if such a person either had never taken up smoking or had quit smoking cigarettes. No sound, scientific thinker would deny the validity of this *possible* explanation of the observed findings. Indeed such a possibility must always be considered in problems such as this one. But it would be the height of folly to forget the *other* possibility, which is *at least* equally likely, that cigarette smoking *is* one of the direct causes of an increased incidence rate of clinical coronary heart disease. In scientific medical problems such as this one the demonstration of a positive association between two variables, e.g. cigarette smoking and coronary heart disease incidence rate, is an excellent *first* step. Whether the first item (cigarette smoking) causes the second item (clinical coronary heart disease) or whether both items are separately caused by some third factor (cigarette smoking and coronary heart disease both being separate results of the metabolic makeup or personality makeup of the individual) can best be considered through appropriate further studies What is of prime importance is the realization that the clear-cut demonstration of a marked association between heavy cigarette smoking and subsequent clinical coronary heart disease is a monumental step forward in the elucidation of factors important in the development of coronary heart disease. Even if it should develop that cigarette smoking is *not* an actual cause of coronary heart disease, the information developed could not help but to lead to identification of *some* factor about smokers of cigarettes that leads them to show an inordinate average susceptibility to clinical coronary heart disease. Valuable leads such as this one are not so easily found as to allow for casual or summary dismissal of their importance.

TABLE XXXIX

Lipoprotein Levels and Atherogenic Index Values in Smokers and Non Smokers*

MEN (Category and Number of Men)	Mean S_f0-12 mg/100ml	Mean S_f12-20 mg/100ml	Mean S_f20-100 mg/100ml	Mean S_f100-400 mg/100ml	Mean Atherogenic Index (units)	Average Number of Cigarettes Per Day
486 men who never smoked	336.8	18.6	81.7	49.5	66.9	0
99 men who smoke fewer than 10 cigarettes per day	316.7	48.2	86.0	43.5	67.0	3.7
315 men who smoke 10-19 cigarettes per day	352.2	47.1	91.7	50.2	69.6	12.7
673 men who smoke more than 20 cigarettes per day	361.5	50.2	93.1	49.3	71.1	22.6
217 men who had given up cigarette smoking	326.7	47.3	87.8	52.8	66.8	0
126 men who smoked pipes or cigars or both, but no cigarettes	335.7	48.0	90.6	59.6	68.4	0
WOMEN (Category and Number of Women)						
128 women who never smoked	303.0	32.7	51.7	14.6	48.5	0
33 women who smoke fewer than 10 cigarettes per day	299.9	30.7	49.7	14.1	47.3	4.5
66 women who smoke between 10 and 19 cigarettes per day	318.8	36.1	51.1	12.1	49.6	12.1
45 women who smoke more than 20 cigarettes per day	325.0	39.4	47.7	10.9	49.5	21.0
15 women who had given up cigarette smoking	275.7	29.8	46.6	13.0	43.9	0

*Since the mean age of the various groups of men ranged from 32.6 to 36.5 years, all values were adjusted to 35.0 years. Similarly, for women all values were adjusted to 30.0 years

with extension and confirmation of the findings now in 2201 persons. These individuals were asked to fill out a questionnaire concerning their past and present smoking habits at the time they were undergoing a routine periodic medical examination at their place of employment. These persons had no idea of the purposes to which the questionnaire might be put nor were they aware of other measurements being made for correlation studies with the smoking history. It seems virtually certain that studies of the relationship of smoking habits with serum lipoprotein levels, conducted in this manner, could not conceivably been systematically biassed in one direction or another. In another part of this medical examination blood pressures were measured in a routine fashion and a sample of blood was withdrawn for lipoprotein and other biochemical analyses. The smoking history questionnaire provided data adequate to subdivide the entire population sample into those who never had smoked, those who smoked cigarettes (divided into sub-categories dependent upon the average number of cigarettes smoked per day), those who had been smokers of cigarettes but who had quit smoking, and those who smoked cigars and/or pipes, but not cigarettes. The lipoprotein and atherogenic index findings for the various categories of smokers and for non-smokers are presented in Table XXXIX Cigarette smokers among the men show highly significant elevations of s_f0-12 and s_f20-100 lipoproteins and of the atherogenic index in comparison with those men who never had smoked Further the group smoking cigarettes heavily (20 or more per day) showed higher values of these variables than did those who smoked fewer than 20 cigarettes per day. These data establish conclusively that cigarette smoking is positively associated with elevation in Atherogenic Index values and hence, that at least part of the association of cigarette smoking with a high incidence rate of coronary heart disease would be expected as a result of the cigarette smoking-atherogenic index relationship. Quantitative assessment of how large this part is will be made below

It is, of course, not unexpected that there will be those who can say that these data do not *prove* that cigarette smoking *causes* the observed elevation in s_f0-12 and s_f20-100 lipoproteins

TABLE XXXIX

LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES IN SMOKERS AND NON SMOKERS*

MEN (Category and Number of Men)	Mean S_f0 12 mg/100ml	Mean S_f12 20 mg/100ml	Mean S_f20-100 mg/100ml	Mean S_f100 400 mg/100ml	Mean Atherogenic Index (units)	Average Number of Cigarettes Per Day
486 men who never smoked	336.8	48.6	81.7	49.5	66.9	0
99 men who smoke fewer than 10 cigarettes per day	316.7	48.2	86.0	43.3	67.0	3.7
315 men who smoke 10 19 cigarettes per day	352.2	47.1	91.7	50.2	69.6	12.7
673 men who smoke more than 20 cigarettes per day	361.5	50.2	93.1	49.3	71.1	22.6
217 men who had given up cigarette smoking	320.7	17.3	87.8	52.8	66.8	0
126 men who smoked pipes or cigars or both, but no cigarettes	335.7	48.0	90.6	59.6	68.4	0
WOMEN (Category and Number of Women)						
128 women who never smoked	303.0	32.7	51.7	14.6	48.5	0
33 women who smoke fewer than 10 cigarettes per day	299.9	30.7	19.7	14.1	47.3	4.5
66 women who smoke between 10 and 19 cigarettes per day	318.8	36.1	51.1	12.1	49.6	12.1
45 women who smoke more than 20 cigarettes per day	325.0	39.4	47.7	10.3	19.3	21.0
13 women who had given up cigarette smoking	275.7	29.8	16.6	13.0	13.9	0

* Since the mean age of the various groups of men ranged from 32.6 to 36.3 years, all values were adjusted to 35.0 years Similarly, for women all values were adjusted to 30.0 years

and in atherogenic index value. To be sure there does exist the *possibility* that persons of certain metabolic types or personality types may smoke more cigarettes than others and may show higher atherogenic index values than others and that the observed association of cigarette smoking with atherogenic index simply reflects such personality and metabolic types. But the existence of this as a *possibility* does not make it the *reality* hoped for by some, for it is at least equally likely (and from additional evidence much more than equally likely) that cigarette smoking *causes* the observed elevation in S_f0-12 and S_f20-100 lipoproteins

FILTER-TIP CIGARETTES VERSUS REGULAR CIGARETTES

The tobacco industry has put a great deal of effort into a campaign to induce cigarette smokers to switch to filter-tip cigarettes. There can be little doubt but that the individual smoker who chooses a filter-tip cigarette is influenced to do so by his hope that any potentially adverse effects of cigarette smoking upon health may be mitigated through the use of filter-tip cigarettes. It is of interest, therefore, to know whether or not filtering smoke through the commonly available filter tip cigarettes alters in any way the association of cigarette smoking with serum lipoprotein and atherogenic index values. The questionnaires utilized in the above-described study specifically requested information concerning the brand of cigarette smoked and whether or not the cigarette was of a filter-tip type. For purposes of analysis all non-filtered brands are considered here as one group, all filtered brands as another group. While this does not allow comparison of possible efficiency of one filter-tip with another, it does provide a measure of the effect of filtration in the form utilized by a reasonable cross-section of cigarette smokers. The comparison data are presented in Table XL No significant differences in lipoprotein levels or atherogenic index values can be demonstrated between those cigarette smokers using the usual group of filter-tip cigarettes and those using the unfiltered brands. With respect to that part of the association of cigarette smoking and coronary heart disease that arises through the association of cigarette smoking with Atherogenic Index val-

TABLE XL

Serum Lipoprotein Levels and Atherogenic Index Values in Smokers of Filter-Tip Cigarettes Versus Smokers of Regular (Non-filtered) Cigarettes*

Category	Mean S_f 0 12 mg/100ml	Mean S_f 12 20 mg/100ml	Mean S_f 20 100 mg/100ml	Mean S_f 100-400 mg/100ml	Mean Atherogenic Index (units)	Mean Number of Cigarettes Per Day
254 men who smoked filter-tip cigarettes	364.4	48 8	93 6	54.2	70 9	18.2
833 men who smoked regular (non-filtered) cigarettes	365 6	50 8	91 5	49.1	70 6	18 0

* The question concerning filtration was introduced into the latter half of this study. Hence data are available only for 1087 men for this feature. No conceivable bias was introduced by this.

ues, no amelioration of the situation is achieved by a substitution of the filter-tip cigarettes in common use during the 1954-1957 period when this study was done.

PIPE AND CIGAR SMOKING AND SERUM LIPOPROTEINS

Hammond and Horn's report on the association of smoking with coronary heart disease showed a much more striking effect for cigarette smoking than for cigar and pipe smoking, although a low degree of association could be demonstrated for cigar and pipe smoking. The data of Table XXXIX indicate that no significant elevation of any of the lipoproteins or of the atherogenic index was demonstrable in those who smoked cigars and/or pipes but who never had smoked cigarettes. Some possible explanations of the lack of an effect of the use of tobacco in these forms are: (1) a lesser consumption of tobacco in pipe or cigar smokers than in cigarette smokers, (2) a temperature difference in the burning of tobacco in the various forms, or (3) an influence of some component of cigarettes other than the tobacco itself.

REVERSIBILITY OF THE EFFECT OF CIGARETTE SMOKING UPON SERUM LIPOPROTEIN LEVELS

Many of the individuals examined in this study had at one time been smokers of cigarettes but had for a variety of reasons made the decision to quit smoking. Some had quit as recently as a few weeks before the questionnaire and blood sampling, others as long as 10 years before. An analysis was made of the lipoprotein levels of this entire group of 217 quitters of cigarette smoking in comparison with those who never had smoked cigarettes. The data are presented in Table XXXIX No significant difference in level of any of the four classes of lipoproteins or of the atherogenic index can be demonstrated to exist between the group who had quit cigarette smoking and the group who had never smoked cigarettes. *If it is assumed that while the members of the first group had smoked cigarettes they would have shown the elevation in lipoprotein levels characteristic of*

current cigarette smokers, it follows that cessation of cigarette smoking has resulted in a *reduction* in lipoprotein and Atherogenic Index values This would indicate that *whatever* the mechanism is by which cigarette smoking becomes related to elevation of blood lipoprotein levels, it is possible to overcome such elevation by cessation of smoking.

The possibility exists, of course, that the "quitters" of cigarettes represent a special group of persons among the smokers, and that the very fact that they quit smoking "proves" this The argument could be advanced that possibly *these* cigarette smokers never had had the lipoprotein elevation characteristic of cigarette smokers and hence that the absence of an elevation in quitters does not prove *reversibility* of an effect of cigarettes on serum lipoproteins. Such requirements of special types of persons, first, to explain the lipoprotein elevation in cigarette smokers, and next, to explain the effect of cessation of smoking begin to multiply the number of metabolic or personality make-ups required and render such *possible* explanations of all the findings very remote in comparison with the more plausible one that cigarette smoking is a causative agent in lipoprotein elevation and that, hence, removal of the causative influence removes the effect, as has been experimentally observed

CIGARETTE SMOKING AND BLOOD PRESSURE LEVELS

Physiologists and pharmacologists have long been interested in the possible influence of tobacco and some of its chemical constituents upon such vital measurements as the blood pressure level Many of the studies that have been reported have focussed upon the relatively acute effects of smoking upon the blood pressure Such information is extremely useful, but needs supplementation by studies of possible chronic effects of cigarette smoking upon the habitual blood *pressure* of individuals.

In direct investigations of the acute effect of cigarette smoking upon the diastolic blood pressure level of habitual smokers Roth[69] found that her subjects showed an average rise in diastolic pressure of 14 mm Hg above a baseline average value of 69 mm Hg during the actual act of smoking

ues, no amelioration of the situation is achieved by a substitution of the filter-tip cigarettes in common use during the 1954-1957 period when this study was done.

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sustained effect of habitual cigarette smoking upon blood pressure level exists.

QUANTITATIVE EVALUATION OF THE RELATIONSHIP OF CIGARETTE SMOKING WITH INCIDENCE RATE OF CLINICAL CORONARY HEART DISEASE

The objective of determination of the presence or absence of an intrinsic, independent effect of cigarette smoking per se upon coronary heart disease can now be realized. First, it is necessary to assess what part of the overall effect can be explained both through the association of cigarette smoking with atherogenic index values and through that of cigarette smoking with blood pressure levels. The statistical calculations of Hammond and Horn[70] showed that regular smokers of 40 cigarettes per day (2 packs) show approximately 2.2 times as high an incidence rate of clinical coronary heart disease as do non-smokers. From the direct measurements of the relationship of cigarette smoking with lipoprotein level and atherogenic index values, smokers of 40 cigarettes per day experience an average elevation in Atherogenic Index value of 8.3 units. For men in the 40-59 year age bracket, this would mean an Atherogenic Index value of approximately 83.8 units for smokers of 40 cigarettes per day contrasted with a value of 75.5 units for non-smokers. Reference to Table XVI (Chapter V) indicates that the relative incidence rate of coronary heart disease for these atherogenic index values is 4.82/3.34, or a 1.44- fold increase in coronary heart disease incidence rate for smokers of 40 cigarettes per day compared with that for non-smokers. But this is the increase in expected incidence rate taking into account only the association of cigarette smoking with atherogenic index. Complete evaluation of the expected incidence rate in smokers *requires* also an accounting of the blood pressure effect.

Since the data described above show *no sustained* effect of cigarette smoking upon diastolic blood pressure level, the considerations need to deal only with the acute effects of cigarette smoking upon the diastolic blood pressure. In the chapter of this book (Chapter VII) where the relationship of age with

secutively. However, within approximately five minutes the diastolic pressure level had returned to the pre-smoking base-line value. Therefore, it is clear that, while smoking, the average cigarette smoker does experience a rise in diastolic blood pressure, but the effect wears off very rapidly following the actual act of smoking.

The rapid decay of the effect of smoking cigarettes upon the blood pressure does not preclude the possibility that habitual smoking of cigarettes may produce some sustained rise in diastolic blood pressure. However, direct studies of this question, reported below, indicate that no such sustained effect upon blood pressure is demonstrable. This was shown in the same group of 2201 consecutive employed persons who were questioned concerning smoking habits and whose lipoprotein levels were measured. The data relating blood pressure values to various categories of smoking habits are presented in Table XLI. Since the blood pressure measurements in this study were made at least 15 minutes after the act of smoking a cigarette in those who may have smoked prior to the medical examination, the type of acute effect found by Roth should not have influenced these observations. The absence of any demonstrable deviation in the mean diastolic blood pressure for habitual cigarette smokers contrasted with persons who had never smoked indicates that no

TABLE XLI

DIASTOLIC BLOOD PRESSURE LEVELS IN SMOKERS AND NON-SMOKERS*

Category	*Mean Diastolic Pressure** (mm Hg)*
486 men who never smoked	71.5
99 men who smoke fewer than 10 cigarettes per day	71 3
315 men who smoke 10 to 19 cigarettes per day	70 6
673 men who smoke more than 20 cigarettes per day	70 6
217 men who had given up cigarette smoking	70 7
126 men who smoked pipes or cigars or both, but no cigarettes	70 3

* The values of mean diastolic pressure were all corrected by the very small correction necessary to adjust to 35 0 years of age for all groups

** These pressures were taken reclining a minimum of 15 minutes after the last cigarette was smoked, if the examinee smoked at all

This means that the combined effect of elevation of atherogenic index and diastolic blood pressure leads to the prediction of a 1.8-fold incidence rate of clinical coronary heart disease in smokers of 40 cigarettes per day in comparison with non-smokers. This is to be compared with the 2.2- fold incidence rate actually observed by Hammond and Horn. It appears quite clear that the effect of cigarette smoking on coronary heart disease incidence rate is wholly, or nearly wholly explained by the elevation in atherogenic index and diastolic blood pressure in cigarette smokers There cannot be much residual independent status of cigarette smoking beyond these mechanisms.

Those who have quit cigarette smoking show a coronary disease incidence rate between those of smokers and non-smokers[70] The lipoprotein findings plus the accumulation concept for coronary disease risk predict precisely this result, if reversibility of *established* risk is not complete.//

coronary heart disease incidence rate was discussed, it was pointed out that all the available evidence indicates that the blood pressure operates as an *accumulative* factor over time rather than as an instantaneous factor. Thus a particular elevation of blood pressure operating over two years would accumulate twice as much toward the risk of ultimate clinical coronary heart disease as would that same elevation in pressure operating over one year. In the absence of any information to the contrary, the most reasonable approximation to the effect of blood pressure elevation for much shorter intervals of time is to consider an accumulation proportional to the time interval involved. Thus, in this case, the knowledge exists from Roth's data[69] that the mean diastolic blood pressure is elevated 14 mm Hg during cigarette smoking. The average duration of this effect is approximately 10 minutes per cigarette. Therefore, a person who smokes 40 cigarettes per day would show such a blood pressure elevation for 40x10, or 400 minutes per day, or about 7 hours per day out of every 24 hours *An elevation of diastolic blood pressure of 14 mm Hg for 7* hours out of 24 hours would correspond to an average elevation of pressure of 7/24 of 14, or 4.1 mm Hg spread over each day. This is the average increase in diastolic blood pressure that can be used to estimate the increase in coronary heart disease incidence rate resulting from the association of acute blood pressure rises with cigarette smoking. The average blood pressure of 40-59 year old men is 74.7 mm Hg, and with a 4.1 mm rise, the cigarette smokers would show an average pressure of 78.8 mm Hg. From Table XIV (Chapter V) this rise in diastolic blood pressure corresponds to a 3.94/3.16, or 1.25-fold increase in coronary heart disease incidence rate, which is the increased incidence rate anticipated for smokers of 40 cigarettes per day as compared with non-smokers.

The *overall* comparison of the coronary heart disease incidence rate for smokers of 40 cigarettes per day and for non-smokers is determined by multiplying the increased incidence rate due to the atherogenic index effect by that for the diastolic blood pressure effect. Therefore, the factor of 1.44 (for the atherogenic index effect) is to be multiplied by 1.25 (for the diastolic blood pressure effect), giving an overall factor of 1.80

the extent to which diabetes mellitus might predispose to excessive coronary heart disease today, it would be a matter of some urgency to know with what kind of people these past reports have been dealing. It is no less important to know today when one discusses diabetics with what type of people one is dealing. Unfortunately so many of the impressions concerning diabetes mellitus arise either from hospital statistics or clinical statistics that it is extremely difficult to know accurately the incidence of such complications as coronary heart disease in the diabetic population as a whole rather than in some select part of the diabetic population which finds itself going to a clinic or a hospital. This very fact alone may bias the data such as to lead to an erroneous impression concerning complications of the diabetic state. A variety of complaints may ultimately lead a person with a disease such as diabetes mellitus to seek care in a medical clinic, one of which complaints might be angina pectoris or other manifest coronary heart disease. Hence, the analysis of hospital statistics or clinic statistics with respect to the incidence of coronary heart disease in diabetes mellitus may be grossly misleading as an index to the status of diabetics in the population-at-large. Perhaps the most effective way to start consideration of this problem is to look back at the pre-insulin period. In the pre-insulin period we had what might be called essentially a homogeneous population of diabetics at least with respect to the one fact that none of them were being treated with insulin, which can no longer be said at the present time. During that period it appears reasonably certain that coronary heart disease and sequelae of arteriosclerosis in other vascular beds was more frequent in the diabetic subjects than in the population-at-large. Even during that period the estimate of the frequency of such disease in the diabetics must have been biassed by the fact that certainly the more severe cases and those with complications most readily found their way into the hospital and clinic populations from which coronary disease statistics were derived for the diabetic. Still, for the [illegible] period, we can look [illegible] concerning such pati[illegible] [illegible]ermine what might have been expected then with respect to coronary heart disease.

Chapter XII

THE RELATIONSHIP OF DIABETES MELLITUS WITH CORONARY HEART DISEASE

THE OPINION is still widely held in medical circles that diabetes mellitus is a disorder characterized by an excessive incidence of premature coronary heart disease. Indeed it has often been stated by medical authorities that, since diabetes mellitus itself need no longer be a fatal disease because of the use of insulin or some of the recent substitutes for insulin therapy, the diabetic now dies of the complications of arteriosclerosis, among which coronary heart disease is prominent. The crucial question at hand is "To what extent does the diabetic die of coronary heart disease earlier in life than does any member of the population-at-large? If the diabetic is protected against death from diabetic acidosis and coma and therefore becomes essentially a member of the population-at-large (but *with* diabetes), one could anticipate that coronary heart disease may be at least as frequent among diabetics as it would be among other members of the population. Since coronary heart disease occurs so frequently in the population-at-large, it is not surprising that physicians should run into many diabetics who develop coronary disease, ultimately including between ¼ and ½ of them. But if this frequency of heart disease is no greater in diabetics than in the population-at-large, then the impression that diabetes mellitus is a predisposing factor *as of today*, might be erroneous.

Oft quoted in support of the concept of the excessive frequency of coronary heart disease in diabetes mellitus are data published in the literature between 1930 and 1950 and based upon the consideration of persons who were in their sixties and seventies during that period. Before reaching a conclusion as to

the extent to which diabetes mellitus might predispose to excessive coronary heart disease today, it would be a matter of some urgency to know with what kind of people these past reports have been dealing. It is no less important to know today when one discusses diabetics with what type of people one is dealing. Unfortunately so many of the impressions concerning diabetes mellitus arise either from hospital statistics or clinical statistics that it is extremely difficult to know accurately the incidence of such complications as coronary heart disease in the diabetic population as a whole rather than in some select part of the diabetic population which finds itself going to a clinic or a hospital. This very fact alone may bias the data such as to lead to an erroneous impression concerning complications of the diabetic state. A variety of complaints may ultimately lead a person with a disease such as diabetes mellitus to seek care in a medical clinic, one of which complaints might be angina pectoris or other manifest coronary heart disease. Hence, the analysis of hospital statistics or clinic statistics with respect to the incidence of coronary heart disease in diabetes mellitus may be grossly misleading as an index to the status of diabetics in the population-at-large. Perhaps the most effective way to start consideration of this problem is to look back at the pre-insulin period In the pre-insulin period we had what might be called essentially a homogeneous population of diabetics at least with respect to the one fact that none of them were being treated with insulin, which can no longer be said at the present time. During that period it appears reasonably certain that coronary heart disease and sequelae of arteriosclerosis in other vascular beds was more frequent in the diabetic subjects than in the population-at-large. Even during that period the estimate of the frequency of such disease in the diabetics must have been biassed by the fact that certainly the more severe cases and those with complications most readily found their way into the hospital and clinic populations from which coronary disease statistics were derived for the diabetic. Still, for the untreated diabetic, during the pre-insulin period, we can look at some of the scientific clinical evidence concerning such patients to determine what might have been expected then with respect to coronary heart disease.

During the pre-insulin period the availability of therapy other than dietary therapy was essentially non-existent, and during that same period uncontrolled diabetes can be said to have been rampant. To be sure, the obese middle-aged diabetic during that period was in essence no different from the obese middle-aged diabetic of today. We do know that in such cases of diabetes that the correction of diet and of attendant overweight will in many cases lead to an amelioration of the diabetic state, a reduction in, or elimination of, glycosuria, a reduction in hyperglycemia, and clinical well-being wholly without the use of insulin. However, there were many diabetics in whom this favorable set of changes could not be induced by dietetic therapy alone during the period in which insulin was absent from the scene. The occurrence of episodes of severe acidosis and even of coma was a frequent occurrence, with a large number of diabetics dying during such episodes. Diabetic acidosis of severe degree and diabetic coma still occur today although much more infrequently than before, but nevertheless their occurrence provides us with a direct way of observing the type of phenomenon that must have been extremely common during the pre-insulin period. Among the most startling findings in uncontrolled diabetes in acidosis or in coma are those which center around the alterations of blood lipid transport. Indeed it can be stated that no other disease has yet been observed which is capable of producing within a matter of days the massive changes in blood lipid transport that can be observed as a diabetic patient passes from control into decontrol and acidosis, and conversely as a diabetic in coma or acidosis is once more brought under control. These considerations can best start with the diabetic in severe decontrol and acidosis with or without coma Numbers of these patients have been studied with respect to the lipoprotein levels of the various classes involved in coronary heart disease, such as the s_f0-12, s_f12-20, s_f20-100, and s_f100-400 classes, during the phase of severe diabetic acidosis and decontrol and during the phases of return to control[71, 72].

The average patient under these circumstances is characterized by a very, very marked derangement of blood lipoprotein transport which involves a lowering of the s_f0-12 lipoproteins,

TABLE XLII

SERUM LIPOPROTEIN LEVELS IN DIABETIC ACIDOSIS AND COMA

Case	Age (years)	Sex	Clinical State	S_f 0-12 mg/100ml	S_f 12-20 mg/100ml	S_f 20-100 mg/100ml	S_f 100-400 mg/100ml	Atherogenic Index (units)
1	37	F	Marked Acidosis No coma Cutaneous Xanthomata	195	155	1120	3739	897
2	44	F	Acidosis and Coma	172	65	343	383	156
3	55	F	Acidosis No coma Cutaneous Xanthomata	235	54	1082	1622	506
4	21	M	Acidosis Semi coma	74	9	334	865	219
5	11	F	Acidosis Semi coma	0	0	416	700	195
6	21	F	Acidosis No coma	179	81	656	647	260
7	39	F	Acidosis Coma	408	139	264	291	162
8	35	M	Acidosis Semi coma	101	40	20	7	52
9	52	F	Acidosis No coma	356	105	164	72	95
10	13	F	Acidosis No coma	226	91	105	31	63
			Grand Mean for 10 cases	224.6	74.2	450.4	835.7	260.5

accompanied by a massive elevation of the lipoproteins of higher flotation classes, including those of the S_f20-100 class, the S_f100-400 class, and lipoproteins of even higher classes all the way out to those known as chylomicrons. In Table XLII are presented the initial findings available for a series of diabetics who were in the hospital in severe acidosis with or without coma. It can be noted that 7 out of 10 of these patients showed a marked derangement in lipoprotein transport of the type just characterized. The mean values of the four lipoprotein classes for all ten cases shows the marked depression in S_f0-12 lipoproteins and the massive elevation of the S_f20-100 and S_f100-400 lipoprotein classes. While every diabetic in acidosis does not show a marked derangement of lipoprotein levels, the averages and the distribution of values speak for themselves with respect to the tremendous derangement that can be said to characterize the usual state of diabetic acidosis and severe diabetic decontrol. The average Atherogenic Index value of 260.5 units is between 3 and 4 times the average for adult males or females in the population-at-large. Hence, with respect to the *rate of accumulation* of sub-clinical coronary heart disease (in all probability in the form of an increment in narrowing of the coronary arteries) it can be expected that the average diabetic in the state of acidosis is accumulating sub-clinical coronary heart disease at a phenomenal rate During the pre-insulin period many diabetics probably could not have chronically been this far out of control, but undoubtedly many of them must have been oscillated into and out of states approaching this degree of decontrol. It would be anticipated that during such phases of decontrol they were developing an extensive degree of sub-clinical coronary heart disease It is not necessary for diabetics to be in a state of coma or semi-coma in order to show the marked derangement in lipoprotein levels which accompanies severe diabetic decontrol. Illustrative changes in lipoprotein levels for one patient followed carefully during her hospital stay while the diabetes was being brought under control are presented in Table XLIII.

A most interesting sequence of events is observed during the period of days, weeks and months during which the diabetic patient has been brought under control from the state of severe

TABLE XLIII

SERIAL LIPOPROTEIN STUDIES DURING THE THERAPY OF DIABETIC ACIDOSIS IN A 37 YEAR OLD PATIENT

Day After Hospital Admission	*Clinical State*	S_f *0-12 mg/100ml*	S_f *12-20 mg/100ml*	S_f *20-100 mg/100ml*	S_f *100-400 mg/100ml*	*Atherogenic Index (units)*
0	In acidosis and coma	195	155	1120	3739	897
4th day	Out of acidosis	441	352	1912	1530	714
9th day	In diabetic control	744	428	1277	685	495
14th day	In diabetic control	939	338	670	139	295
29th day	In diabetic control	614	131	495	228	211
43rd day	In diabetic control	531	148	432	132	178
50th day	In diabetic control	616	150	332	152	173
56th day	In diabetic control	549	108	150	31	105
—Discharged from hospital—						
116th day	Supposedly in diabetic control at home but showing acetonuria	452	237	988	461	340
400th day	Supposedly in diabetic control at home but showing acetonuria	276	188	968	840	377

diabetic acidosis. As the diabetes is brought under control through usual medical measures, including insulin among others, the massively elevated levels of lipoproteins above s_f400 and of the s_f100-400 class are noted to decline as a very early phenomenon. During the time when the levels of these lipoproteins are falling, there is first a rise in concentration of those of successively lower flotation classes. Thus, as the s_f100-400 lipoprotein levels start falling, the s_f20-100 lipoprotein levels show a rise in concentration, as though there might actually be a transformation occurring from the lipoproteins of the higher flotation classes to those of successively lower flotation classes. With the passage of a little more time measured in days the s_f100-400 lipoprotein levels fall still further and then the s_f20-100 lipoprotein levels, which at first were rising, begin to decline, accompanied first by an increase in the s_f12-20 lipoproteins and finally also in the s_f0-12 liproproteins. Still further along in this entire evolutions of events the s_f20-100 and s_f100-400 lipoproteins may approach values of the order of these observed in the population-at-large (even lower than for many persons in the population-at-large). At this time the s_f0-12 lipoprotein levels are massively elevated in comparison with the levels encountered in the members of the population-at-large. Finally, with further maintenance of diabetic control, the massive elevation of the s_f0-12 lipoprotein levels recedes, leaving the diabetic ultimately with the type of pattern that characterizes him or her during a state of control. The lipoprotein distribution in diabetic control is not a standard one, since there is variability among diabetics in control just as there is variability in the levels of the various lipoprotein classes among the members of the population-at-large All the events described above have been observed in several diabetic patients going from the stage of severe acidosis and decontrol back to control, so that it is by no means the happenstance of a single, particular diabetic patient. This sequence of changes can be regarded as a general trend which characterizes diabetes during these stages Furthermore, certain patients who have been brought out of severe acidosis have been observed for a period of months and years while attempting to control their diabetes at home. The patient described in Table XLIII was observed

during a repeat episode of acidosis (although clinically a much milder episode of acidosis than during the initial study). During this second, relatively mild episode of acidosis the patient showed a reversion to a lipoprotein distribution intermediary between that observed in the earlier marked decontrol stage and that in the stage of control during her hospital stay. This general train of events can be anticipated to have been extremely common during the period before the introduction of insulin, even though lipoprotein values were not available during that time to delineate the changes

That a disease process such as the accumulation of subclinical coronary heart disease was, in all probability, going on excessively during such a period is supported by auxiliary (though not necessary) evidence concerning the development of xanthomatosis in the diabetic patient. Xanthoma diabeticorum, which is more commonly referred to as *eruptive* xanthoma diabeticorum is a lesion occurring in the skin histopathologically closely akin to the arterioatherosclerotic lesions of the coronary artery and of other medium and large arteries There are pathologists who would claim the ability to distinguish a xanthomatotic lesion from an athero-arteriosclerotic lesion even though both lesions are grossly similar. One might question the ability to make this distinction if the surrounding landmarks of tissue such as the coats of the vessel in the case of the arteriosclerotic lesion or the overlying skin in the case of the skin lesion were stripped away leaving the bare lesion Under these circumstances it can be fairly well assured that pathological differentiation of the lesions would be much less readily made There are abundant reasons to consider that the pathogenesis of these two lesions is extremely similar. Diabetic patients do not commonly show the lesion of eruptive xanthoma diabeticorum during diabetic control. Indeed the very term, eruptive, indicates the relatively acute onset of development of such lesions and the acute nature of the entire process These lesions erupt during some aspect of the phase of severe diabetic decontrol and acidosis and may persist and increase during the stage of marked diabetic acidosis and coma It is to be noted that such lesions occur in those cases who have enormously elevated lipoprotein levels of the S_f12-400 class as part of their

manifestation of the entire phenomenon of diabetic acidosis and decontrol. There is very little doubt that the massively elevated lipoprotein levels of these classes are directly associated with the development of the eruptive xanthoma diabeticorum. Furthermore, as the diabetic is brought back into control, and out of acidosis, and as the lipoprotein levels recede toward much more normal levels, the lesions of xanthoma diabeticorum no longer develop de novo. Old lesions, which had appeared during the stage of massive lipoprotein elevation, begin to decrease in size, and in a period of weeks and months, trailing the lipoprotein level lowering, the lesions generally disappear completely, leaving in most areas very little if any trace of the xanthomata. This xanthomatous lesion, which develops in association with extremely high lipoprotein levels, is a manifestation of what can happen in the skin if lipoprotein levels are high enough. For a process such as this it appears unquestionable from a variety of types of evidence that certain regions of the body differ with respect to receptivity to formation of the lipid-filled lesions of this character. It is not surprising, therefore, to find that skin may be one of the less receptive areas as compared with tissues in general, such as arterial walls, and that the lesions which are seen in the skin form only when the lipoprotein levels are massively elevated There is no reason to consider that the lipoproteins are different in kind from those which exist at lower levels in the population-at-large, but rather that they are so massively elevated in concentration during the state of diabetic acidosis that the skin lesions form The corresponding arterial lesions we can feel quite certain form at much, much lower lipoprotein levels in the blood since arteriosclerosis proceeds at a fair rate in the population-at-large with more moderate lipoprotein levels

Thus, during a phase of diabetic decontrol and acidosis with its massive elevation of lipoprotein levels, it can be anticipated that, whatever rate of coronary atheroma development usually existed in such an individual, it will have been massively accelerated during the periods of decontrol with the fabulous rises in lipoprotein levels which accompany such periods. The diabetic during the pre-insulin period must have been in and out of phases of severe acidosis and may have been midly acidotic for

very long periods of time, since full control of the diabetes was not possible in that era without the assistance from insulin therapy. Therefore regression of arteriosclerotic lesions that might have occurred (analogous to the regression of the xanthomatous lesions which occurs when the lipoproteins are lowered in an acidotic diabetic), may have been inhibited because of the maintenance of mild acidosis. From studies of other xanthomatoses, such as xanthoma tuberosum, it is known (see Chapter X) that the longer standing lesions are no longer primarily the lipid-laden lesions, but instead have accumulated a considerable amount of fibrous tissue. During the regression of such longer-standing lesions in xanthoma tuberosum which accompanies lowering of lipoprotein levels, the lipid element of the lesion regresses very markedly and may disappear entirely, but the fibrous element does not. To what extent the fibrotic element in the arteriosclerotic lesion develops more rapidly or less rapidly than in the xanthomatotic lesion cannot be stated, but it is certain to develop at some reasonably comparable pace. Therefore, for the diabetic who has spent a fair part of his life in the acidotic state, or decontrol state, there will be expected, with each deposition of lipid in arterial lesions, a development of fibrosis and hence some accumulation of a partially or wholly irreversible part of the lesion even though the diabetes has been brought under control by medical measures.

The entire discussion of the xanthomatosis of diabetes, its relationship with the arteriosclerotic lesion, and the relationship of both of these with the progression of sub-clinical coronary heart disease in patients with diabetes is *ancillary* evidence. As stated earlier in this book, because of controversies concerning the primacy of events in the development of the arteriosclerotic lesion, evidence pertaining to arteriosclerosis would not be utilized as basic support for demonstration of the factors involved in the development of sub-clinical and clinical coronary heart disease. However, where ancillary evidence deriving from pathology might help understand a particular issue, such ancillary evidence should not be neglected. In this case there exists no need to utilize the ancillary evidence as the basic proof or evidence for the phenomenon at hand, but it does lend further consistency to

manifestation of the entire phenomenon of diabetic acidosis and decontrol. There is very little doubt that the massively elevated lipoprotein levels of these classes are directly associated with the development of the eruptive xanthoma diabeticorum. Furthermore, as the diabetic is brought back into control, and out of acidosis, and as the lipoprotein levels recede toward much more normal levels, the lesions of xanthoma diabeticorum no longer develop de novo. Old lesions, which had appeared during the stage of massive lipoprotein elevation, begin to decrease in size, and in a period of weeks and months, trailing the lipoprotein level lowering, the lesions generally disappear completely, leaving in most areas very little if any trace of the xanthomata. This xanthomatous lesion, which develops in association with extremely high lipoprotein levels, is a manifestation of what can happen in the skin if lipoprotein levels are high enough. For a process such as this it appears unquestionable from a variety of types of evidence that certain regions of the body differ with respect to receptivity to formation of the lipid-filled lesions of this character. It is not surprising, therefore, to find that skin may be one of the less receptive areas as compared with tissues in general, such as arterial walls, and that the lesions which are seen in the skin form only when the lipoprotein levels are massively elevated. There is no reason to consider that the lipoproteins are different in kind from those which exist at lower levels in the population-at-large, but rather that they are so massively elevated in concentration during the state of diabetic acidosis that the skin lesions form. The corresponding arterial lesions we can feel quite certain form at much, much lower lipoprotein levels in the blood since arteriosclerosis proceeds at a fair rate in the population-at-large with more moderate lipoprotein levels.

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showing effects upon their coronary heart disease risk due to the time they spent as diabetics during the pre-insulin period. This point is commonly overlooked by authors writing in the 1940's and 1950's, especially concerning diabetics in the seventh, eighth, and ninth decade of life and their incidence of coronary and other vascular disease. Such evidence can hardly be utilized to provide the requisite information concerning the fate of diabetes of today under good control. Therefore it is necessary to reevaluate completely for the diabetic of the present era what the real situation is with respect to the incidence of coronary heart disease.

THE INCIDENCE OF CORONARY HEART DISEASE IN DIABETES MELLITUS IN THE POST-INSULIN PERIOD

Ideally, the determination of any possible increase in incidence rate of clinical coronary heart disease in diabetics during the post-insulin period would require the following evaluations:

(1) The real incidence of diabetes mellitus in the population-at-large at various ages and for both sexes
(2) Follow-up observations of an adequately large series of such diabetics, random in the population-at-large, to determine the age specific incidence rate of clinical coronary heart disease for both sexes
(3) Follow-up of an adequately large sample of the non-diabetic population-at large to determine the age-specific incidence rate of clinical coronary heart disease in both sexes.
(4) Assurance that the diabetic persons had not spent a large share of their life in the pre-insulin era This would not be a serious problem in data collected now, although it certainly has been in literature reports of the past few decades

What is available now in the way of evidence falls short by a tremendous margin of such evaluations. The pitfalls of utilization of clinic or hospital patients or of hospital autopsy data are many and have been alluded to in the earlier discussion above Thus comparison of the frequency of occurrence of diabetes mellitus in a hospital series of myocardial infarctions with the prevalence of diabetes in an age and sex-matched sample of the

the concepts involved. All the evidence concerning diabetic acidosis is self-sufficient in terms of the direct relationship of blood lipoproteins to the development of sub-clinical coronary heart disease without the intermediacy of the arteriosclerotic or xanthomatotic lesions. Since it has been shown before (see Chapter V) that the higher the lipoprotein level, the greater is the accumulation rate of sub-clinical coronary disease, and hence *the greater ultimate risk of clinical coronary disease,* it can be stated that a diabetic in acidosis, with the lipoprotein levels which characterize that state, would have been accumulating sub-clinical coronary heart disease at a tremendously increased rate in comparison with the diabetic in control or with the non-diabetic. Hence the frequent existence of severe decontrol of diabetes during the pre-insulin period should have markedly increased the predisposition of diabetic patients to the development of early and severe coronary heart disease. This is completely consistent with the numerous literature reports of a high incidence of coronary heart disease in the pre-insulin period. *However, the pre-insulin period is over* Indeed, we are in a phase now where insulin itself is being compared with numerous other drugs that may replace it in part at least in the management of certain diabetic patients All the considerations of coronary heart disease incidence rate for the pre-insulin period, with its high frequency of acidosis and coma, are of very little moment for the present era. The crucial question is whether or not diabetes as it is usually encountered today is still characterized by any excessive frequency of coronary heart disease In order to assess this issue critically several points must be carefully considered First, when statistical data concerning the incidence of coronary heart disease in diabetic patients between 1930 and 1950 are reviewed, it must be remembered that many of such diabetics (especially those in the older age groups) must have spent a *considerable portion of their life in the pre-insulin period* or in the early insulin period when insulin was not as widely used as it has been in more recent years. Hence, if at least *part* of *the accumulation of sub-clinical coronary heart disease* is not reversible, it would be expected that some of the diabetics of the 1930-1950 era, especially those of older age groups, would still be

showing effects upon their coronary heart disease risk due to the time they spent as diabetics during the pre-insulin period. This point is commonly overlooked by authors writing in the 1940's and 1950's, especially concerning diabetics in the seventh, eighth, and ninth decade of life and their incidence of coronary and other vascular disease. Such evidence can hardly be utilized to provide the requisite information concerning the fate of diabetes of today under good control. Therefore it is necessary to reevaluate completely for the diabetic of the present era what the real situation is with respect to the incidence of coronary heart disease.

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What is available now in the way of evidence falls short by a tremendous margin of such evaluations The pitfalls of utilization of clinic or hospital patients or of hospital autopsy data are many and have been alluded to in the earlier discussion above. Thus comparison of the frequency of occurrence of diabetes mellitus in a hospital series of myocardial infarctions with the prevalence of diabetes in an age and sex-matched sample of the

non-diabetic population can be seriously biassed. For example, a hospital with a well-known and well-managed diabetes clinic service is likely to have a higher proportion of diabetics in its overall clientele than characterizes the incidence of diabetes mellitus in the population-at-large. In such a clinic there will exist a high index of awareness of coronary heart disease among their diabetics. This together with the loading of the overall clientele with diabetics will tend to produce a falsely high incidence of diabetes mellitus in a myocardial infarction series from such a hospital, if that incidence of diabetes is compared with the incidence of diabetes in the population-at-large. Similarly, if a hospital draws upon one group, ethnically or on some other basis, the incidence of diabetes in a myocardial infarction series cannot and should not be justifiably compared with that in the population-at-large. It has been stated in the literature[73] that Jews show a higher prevalence of diabetes mellitus than that for the non-Jewish population. If this be true, it is completely inappropriate to relate the incidence of diabetes in a series of myocardial infarction cases from a Jewish hospital with the incidence of diabetes mellitus in the overall population-at-large.

A survey of the litereature (even avoiding those reports contaminated by diabetics from the pre-insulin period), reveals that the possibilities for bias are large and, unfortunately, subtle enough that efforts to correct for such bias are not particularly fruitful.

However, even with whatever bias exists in the literature reports from clinics and hospitals, it is not unreasonable to try to establish some upper limits to any excessive predisposition of diabetic persons to develop clinical coronary heart disease utilizing such literature data The nature of the biassing errors are in general such as to *overestimate* any excessive risk for diabetics rather than to underestimate it. Wright et al, Master et al, Doscher and Poindexter, and Mintz and Katz have provided data concerning the prevalence of diabetes mellitus among myocardial infarction cases both for their own series and from the literature[34, 74, 28,29]. These prevalence data are reproduced below

	Males	*Females*
Wright, Marple and Beck	7.1% (Based upon 774 cases)	21.2% (Based upon 210 cases)

Doscher and Poindexter	5.1% (Based upon 354 cases)	18.9% (Based upon 80 cases)
Master, Dack and Jaffe	6.7% (Based upon males among 550 cases)	26.0% (Based upon 150 cases)
Mintz and Katz	9.2% (Based upon 392 cases)	27.2% (Based upon 180 cases)
Total cases	1850	650

The best prevalence from all these data is the weighted mean values for all the series, which yields the values, 7.1% of men with myocardial infarction are diabetics and 24.8% of women with myocardial infarction are diabetics. The mean age of such infarction series is approximately 60 years.

From the systematic community study at Oxford, Massachusetts by Wilkerson and Krall[75], the prevalence rates of diabetes mellitus in a population sample at comparable mean ages were:

For men at 60 years of age, 5.2% of the population sample was diabetic
For women at 60 years of age, 7.2% of the population sample was diabetic.

Suppose that the male diabetic at 60 years of age is more prone to develop myocardial infarction than the average male of 60 years of age in the population-at-large. We may set the risk of the diabetic male at x times that of the non-diabetic male. For every case of myocardial infarction per 1000 non-diabetic men, there would be x cases per 1000 diabetic men of the same age. With this information, the data above concerning the incidence of diabetes in 60 year old men in the population-at-large, and the incidence of diabetes in the myocardial infarction series, the value of x can be calculated. The observed ratio of male non-diabetic myocardial infarction cases to diabetic myocardial infarction cases is 92.9 to 7.1. In the population-at-large there would be 5.2 diabetic men for every 94.8 non-diabetic men. Whatever the incidence rate of myocardial infarction is in non-diabetic men, the rate for diabetic men has been set at x times that value. Therefore the number of cases of myocardial infarction arising from the non-diabetic men is (94.8) times (the incidence rate). Out of the same 100 men, the number of cases of myocardial infarction arising from the diabetic men is (5.2) times (the incidence rate) times (x). The ratio of non-diabetic infarction cases to diabetic infarction cases is therefore=

$$\frac{(94.8) \text{ times (Incidence Rate)}}{(5.2) \text{ times (Incidence Rate) times } (x)}$$

The (incidence rate) factor cancels out in this ratio, leaving *94.8 over (5.2) times (x). But this must be set equal to the* observed ratio of 92.9 over 7.1. Therefore:

$$\frac{94.8}{5.2x} = \frac{92.9}{7.1}$$

Solving, it is found that:

$$x = \frac{(94.8)\ (7.1)}{(92.9)\ (5.2)} = \frac{673}{483} = 1.39$$

Therefore, it turns out that, even utilizing data which may be biassed toward overstating the hazard of coronary heart disease in diabetics, the diabetic man at an average age of 60 years *is only 1.39 times as likely to develop coronary heart disease* as is the non-diabetic man of the same age.

In an entirely analogous manner the risk of the diabetic women of 60 years compared with the non-diabetic women is calculated. Here, we have:

$$\frac{75.2}{24.8} = \frac{92.8}{7.2x},\ \text{or}\ x = \frac{(92.8)\ (24.8)}{(75.2)\ (7.2)} = \frac{2301}{541} = 4.25$$

Therefore, the diabetic woman at age 60 years has approximately 4.3 times the risk of coronary heart disease compared with the non-diabetic woman of the same age. It does appear, even allowing for bias, that there really is an appreciably excessive coronary heart disease risk in the 60 year old diabetic woman compared with the woman of the same age in the population-at-large.

IS DIABETES MELLITUS AN INDEPENDENT FACTOR IN DETERMINATION OF CORONARY HEART DISEASE RISK?

Diabetes mellitus is no exception to what must be our general approach to the evaluation of factors associated with coronary heart disease, namely a determination of whether it operates as an *independent, or new,* factor or whether it operates through one of the two basic known factors, the Atherogenic Index, the diastolic blood pressure, or both. Clinically and practically the answer to this question is of vast importance to the physician and to every person who has diabetes mellitus. For, few issues are more crucial than to know whether *anything*

about diabetes per se is involved in acceleration of the development of sub-clinical coronary heart disease. If not, new vistas open both for the physician and the diabetic patient for whom he is the medical counselor.

Evaluation of the extent to which diabetes mellitus may predispose to coronary heart disease through elevation either of Atherogenic Index or diastolic blood pressure, or both, requires some knowledge of the values of these variables in cross-sections of *today's* diabetics Hypertension and overweight are known to be common findings in the older diabetic woman especially, and there is good literature documentation of these findings. The hypertension would itself be a predisposing factor, and the overweight is known from independent studies to be associated with atherogenic index elevation. However, direct data in diabetic persons are still vital. In the course of a large-scale evaluation of lipoprotein levels as a predictive indicator for coronary heart disease (Table IV), the Donner Laboratory studied bloods from several thousand persons of the National Heart Institute evaluation of a cross-section of the community of Framingham, Massachusetts plus certain groups of industrial employees. There were, among these thousands of individuals, a reasonable number of diabetic persons. Of 31 diabetic females, 24 were members of the Framingham Community study, 7 were employees of the Eastman Kodak Corporation and 1 was an employee of the Los Angeles Civil Service Commission Of 69 diabetic males, 32 were members of the Framingham Community study, 20 were employees of the Eastman Kodak Corporation, 11 were employees of the Los Angeles Civil Service Commission, 5 were employees of United Air Lines Corporation and 1 was an employee of the Pan American Airlines Company Probably the overall group of diabetics is as reasonable a cross-section of diabetics as could be obtained for study, short of a mammoth effort It is certainly a better index of *the* diabetic population than a group chosen from a diabetic clinic or hospital The mean Atherogenic Index values and diastolic blood pressures for these diabetics are compared with those for their matched non-diabetic groups in Table XLIV. The elevations in Atherogenic Index for diabetic males versus non-diabetic males and for diabetic females versus non diabetic

females are appreciable and highly significant ($p << 0.01$). The blood pressure *in diabetic males is only slightly above that in the* non-diabetic male and cannot be proven significant. The blood pressure in diabetic women is appreciably and significantly above that for the non-diabetic women.

Risk accounting is performed in the manner described in Chapter V. For the diabetic man, the Atherogenic Index of 97.0 units (Table XVI) corresponds to a coronary heart disease risk of 7.2 times that of the reference Atherogenic Index of 30 units. For the average non-diabetic man the Atherogenic Index of 81.7 units corresponds to a risk of 4.46. Therefore the incidence rate of coronary heart disease in diabetic men of this age is expected to be 7.2 over 4.46 equals 1 61 times that for the non-diabetic man of the same age, *based upon the Atherogenic Index* alone. The blood pressure difference of 2.0 mm between diabetic and non-diabetic men was not provably significant. If it is real, then from Table XIV, the relative risk for diabetic men versus non-diabetic men (for pressures of 87 0 mm and 85 0 mm, respectively) is 5 30 over 4.98 equals 1 06. Therefore from diastolic blood pressure alone, the relative risk for diabetic men is between 1.00 and 1.06 that for non-diabetic men of the same age.

TABLE XLIV

ATHEROGENIC INDEX VALUES AND DIASTOLIC BLOOD PRESSURES IN A CROSS SECTION OF DIABETIC PERSONS AND IN GROUP-MATCHED NON-DIABETIC PERSONS

MEN (69 diabetics)	*Mean Age*	*Mean Atherogenic Index (units)*	*Mean Diastolic Blood Pressure (mm Hg)*
Diabetics	52 8 years	97 0	87 0
Matched Non Diabetic Controls	52 8 years	81 7	85 0
Difference (Diabetics - Non-Diabetics)		+ 15.3	+ 2 0
WOMEN (31 diabetics)			
Diabetics	51 3 years	98 3	93 6
Matched Non-Diabetic Controls	54 3 years	78.2	87 4
Difference (Diabetics - Non Diabetics)		+ 20.1	+ 6 2

The overall, or *net* risk, is obtained by multiplication of that from Atherogenic Index by that from diastolic blood pressure (Chapter V). The overall coronary heart disease incidence rate for diabetic men is therefore predicted to be between 1.0x1.61 and 1.06x1.61, or between 1.61 and 1.71 times as high as that for the age-matched non-diabetic man. This is to be compared with the above described observed relative incidence rates (from myocardial infarction series) of 1.39 times in diabetic men as in non-diabetic men for the same general age range This represents excellent agreement between the observed relative incidence rate and the rate predicted from the combination of Atherogenic Index and diastolic blood pressure. Considering the nature of the material available for such a study, the extent of agreement is close enough so that it can be stated that Atherogenic Index plus blood pressure effects account for the vast bulk, if not all, of the effect of diabetes mellitus in predisposing men to coronary heart disease.

For the diabetic women the average Atherogenic Index of 98 3 units compared with 78.2 units for the age-matched non-diabetic women corresponds (Table XVI) to a relative risk of 7 43 over 3.84, or 1 93 times This accounts only for the contribution to risk from the Atherogenic Index For the diabetic women the average diastolic blood pressure of 93.6 mm Hg compared with 87 4 mm in age-matched non-diabetic women corresponds (Table XIV) to a relative risk of 6.44 over 5 37, or 1.20 times The overall, or net risk, obtained by multiplying that from Atherogenic Index by that from diastolic blood pressure, is 1 93x1 20 = 2 31 This relative incidence rate is to be compared with that observed (myocardial infarction series) of 4 25 times. Thus, this approximate type of analysis indicates that the combination of Atherogenic Index plus diastolic blood pressure accounts for the order of 54% of the overall increased risk for diabetic women compared with non-diabetic women. When consideration is given to the sources of material and the relatively small series of diabetic women available, it is entirely possible that essentially all the excessive risk of coronary heart disease in diabetic women is accounted for by the combined effects of

Atherogenic Index and diastolic pressure. In any event it appears that these effects account for over half of the excessive risk.

These *calculations indicate that for diabetics* as a group the diastolic pressure and the Atherogenic Index together account for the largest share of the excessive heart disease rate experienced. If any other features of diabetes are *of any consequence*, they can at best account only for a small part of the excessive risk. There exists no valid scientific evidence in the literature to support the idea that some intrinsic feature of diabetes *per se* contributes in any way to an increased incidence rate of coronary heart disease among diabetics. Indeed no previous study has ever been reported which attempted to ascertain quantitatively whether or not the diastolic blood pressure elevation and the Atherogenic Index elevation were a sufficient basis for the excessive heart disease risk of diabetics. Speculations are rife concerning the possibility of metabolic and/or structural features surrounding capillary integrity in diabetics but no evidence whatever has come forth to show that such features are of any consequence whatever for the coronary arteries. Reference to the capillary lesions of the retina and the kidney may be wholly irrelevant to the situation in the coronary arteries. Indeed the observation of massive elevation of blood lipoproteins in diabetic retinopathy[76] and in diabetic nephropathy[77] may even suggest that the hyperlipoproteinemia should be considered as a possible contributing precursor of those capillary lesions.

The impression that diabetes *per se must* be a contributing factor to excessive risk of coronary heart disease, over and above Atherogenic Index and blood pressure effects, arises commonly from two erroneous sources. First, physicians are properly impressed that their diabetic patients do experience considerably more frequent coronary heart disease than their non-diabetic patients *Often overlooked, however, is the fact that their* average diabetic patient *is older* than the average person in the population-at-large. Diabetes is a disorder the incidence of which increases sharply with increasing age. Thus, even if consideration is limited to adults in the 30-69 year age range, it is readily demonstrable that the average age of men in the diabetic population is *52.5* years compared with *46.3* years for non-diabetic men,

and 53.1 years for diabetic women compared with 44.1 years for non-diabetic women. Since a 10 year difference in age would of itself lead to a tripling of the incidence rate of coronary heart disease, the fact that diabetics in our population are 6 to 9 years older than non-diabetics would itself lead to an expected rate of coronary heart disease two to three times higher in the diabetics. The way to avoid such erroneous impressions is always to compare groups on an age-specific basis, as was done in the earlier calculations of this discussion

The second erroneous source of the impression that diabetes *per se* must contribute to an excessive hazard of coronary heart disease is the expectation that diabetics would have to show the massive blood lipid elevations of the pre-insulin period. Such blood lipid elevation is *far* from necessary in order to explain excessive risk of coronary heart disease The data of Table XVI show what an increase in risk a rise of 10 Atherogenic Index units means Such rises are not massive at all, and unless the nature of the risk tables is understood, the wrong impression will be gained Indeed, if many diabetics showed the massive blood lipid elevations expected in some quarters, their hazard of coronary heart disease would be vastly above what it now is

PRACTICAL CLINICAL IMPLICATIONS OF THE NATURE OF THE ASSOCIATION OF DIABETES MELLITUS WITH CORONARY HEART DISEASE

Since it appears that Atherogenic Index elevation and blood pressure elevations are the prime contributors to the excessive hazard of coronary heart disease in diabetic patients (as in people in general), some important features of management of the diabetic patient need discussion. These center around (1) the relationship of diabetic control to subsequent evolution of clinical coronary heart disease, and (2) prognostic information for the diabetic patient

DOES STRICT CHEMICAL CONTROL OF DIABETES MELLITUS DECREASE THE HAZARD OF CORONARY HEART DISEASE?

Emotionalism, much more than evidence, has held the stage in this question of the value of strict chemical control of diabetes mellitus for prevention of premature vascular disease. Some rational, unbiased approaches have sorely been needed in this area. Ideally it should be possible to determine the age-specific incidence rate of a complication such as coronary heart disease by observing the fate of diabetics under various types of management regimens. This, it has been shown, is easier to propose than to execute. The questions of comparability of patient material from various clinics, the many medical measures employed over and above diabetic control, and a host of other features have arisen to leave this problem largely unanswered.

It seems reasonable to state that, since lipoprotein levels, Atherogenic Index values and blood pressure together account quantitatively for most of the excessive hazard of coronary heart disease in diabetic patients, one might profitably look at the relationship of chemical control with these variables. The studies of diabetics in acidosis show a marked Atherogenic Index elevation to characterize that state. Therefore, it is quite apparent, without further evidence, that de-control of diabetes to this extent is contra-indicated, as it is on other grounds as well. But this *is* not the real clinical problem. Rather it is the region of hyperglycemia and glycosuria *short of* acidosis that is of importance. The advocates of strict chemical control would try to minimize hyperglycemia and glycosuria, always mindful of course of the necessity of not overstepping into the highly undesirable region of hypoglycemic episodes. Those who oppose strict chemical control have been unconvinced that hyperglycemia and glycosuria, without acidosis, are of much consequence and have, therefore, not been concerned about patients spending most of their time with moderate hyperglycemia and some glycosuria.

Strisower and co-workers[78] have recently presented direct evidence concerning the relationship of chemical control with serum lipoprotein levels and Atherogenic Index values, *in this region short* of acidosis. These studies were performed in a

group of 17 institutionalized diabetic, schizophrenic women on the medical service of a large state hospital. The patients were all ambulatory. Since careful observation was possible for the group, it was deemed feasible to raise or lower insulin dosage in such patients for periods of many weeks or months so as to achieve an alteration in mean fasting blood sugar levels. During such periods of "control" (high insulin dosage) and "decontrol," but without acidosis (low insulin dosage), serial lipoprotein analyses were made. There is no doubt that alteration in insulin dosage provoked alterations in chemical control, for the chronic fasting blood sugar levels in essentially all patients were markedly lowered during high insulin dosage and raised during low insulin dosage The overall findings of the Strisower study are presented in Table XLV. There is a highly significant, appreciable average lowering of the Atherogenic Index associated

TABLE XLV

ALTERATIONS IN SERUM LIPOPROTEINS AND ATHEROGENIC INDEX VALUES IN RELATION TO CHEMICAL CONTROL OF DIABETES (17 PATIENTS)

Variable	*Mean Level** in "Control" Phase	*Mean Level*** in "Decontrol" Phase	*Difference* "Decontrol-Control"
S_f0 12 Lipoproteins (mg/100ml)	385	415	+ 30 ($p < 0.001$)
S_f12 20 Lipoproteins (mg/100ml)	73	71	− 2 (Not significant)
S_f20 100 Lipoproteins (mg/100ml)	93	101	+ 8 ($p < 0.10$)
S_f100 400 Lipoproteins (mg/100ml)	23	32	+ 9 ($p < 0.02$)
Atherogenic Index (units)	72	79	+ 7 ($p < 0.01$)
Mean Fasting Blood Sugar (mg/100ml)	105	191	+ 86 ($p < 0.001$)
Mean Insulin Dosage (units)	49	13	− 36

* Mean values of 150 blood samples representing a total study period of 229 [illegible] weeks

** Mean [illegible]

[illegible] are not complicating factors in

with the lower blood sugars of the "control" (high insulin dosage) phase contrasted with the other phase. These workers showed further that middle-aged patients showed a larger effect than did very elderly diabetic patients. Such data provide sound, biochemical support for the concept that strict chemical control of diabetes is of value in reducing one major factor associated with increasing the risk of premature coronary heart disease. It is hardly necessary to emphasize that this is *not* advocacy of insulin dosages sufficiently high as to provoke frequent episodes of hypoglycemia.

PROGNOSIS FOR THE DIABETIC PATIENT

It is regrettable that the scientifically unsupported notion that *diabetes per se* implies a high risk of premature coronary heart disease should have gained wide credence. The medical literature is replete with statements to the effect that, although diabetics need no longer die of acidosis or coma, they still are doomed to a complication of premature arteriosclerosis The *evidence* is quite otherwise. In the discussion above it was shown in quantitative terms that the major share (if not all) of the excessive risk of a complication such as coronary heart disease arises from Atherogenic Index elevation or diastolic blood pressure, or both. But this is an *average* finding for diabetic patients A particular diabetic patient can have escaped both the lipoprotein-Atherogenic Index elevation and the blood pressure elevation. For this patient there is no reason for the physician to be gloomy with respect to the prognostic outlook nor to generalize the increased risk of diabetes to this patient. If such a diabetic patient can maintain low or moderate Atherogenic Index and diastolic blood pressure values, *his* risk of premature coronary heart disease may be expected to be many times lower than the risk for many persons who are not diabetic. The point is that the physician has available to him valid, measurable criteria that determine, at a minimum, the largest share of the risk of vascular complications, namely the lipoprotein and blood pressure measurements Wide use of such criteria instead of the much less correct generalizations concerning diabetes will provide

exceedingly welcome relief to large number of diabetic patients who fear heart disease as an inevitable result of their being diabetic Furthermore, utilization of these valid criteria of coronary heart disease risk can prove to be invaluable aids to the physician in management of the diabetic, both in the areas of the planning of a regimen and in procurement of the patients' maximum cooperation in the control of his disease.

Chapter XIII

THE THYROID AND CORONARY HEART DISEASE

INTEREST has for decades centered about the question of the inter-relationships of thyroid function, blood lipid levels, coronary arteriosclerosis, and coronary heart disease. The clinical literature on this subject is a maze of confusion, contradictory statements, and sweeping opinions based upon scanty evidence and, in many cases, no evidence whatever. But few problems are of greater importance to the physician interested in coronary heart disease than to know the true status of the role of the thyroid and of thyroid hormone and its congeners. There are *several cogent reasons why this is true, among which are;*

(1) Hypothyroidism, spontaneous or iatrogenically induced elevates blood lipoprotein levels (especially S_f0-12 and S_f12-20), and hence elevates the Atherogenic Index

(2) Desiccated thyroid substance[79], thyroxine[80], and tri-iodothyronine[81] have all been demonstrated to be potent for *lowering blood lipoprotein levels and Atherogenic Index* values, not only in hypothyroid persons *but also* in euthyroid persons.

(3) The classical mode of production of arteriosclerosis in animals, ordinarily resistant, involves the use of thyroid ablation, either surgically, by radiation, or by thiouracil or related drugs

(4) A vast clinical literature indicates that hypothyroidism accelerates development of coronary arteriosclerosis.

BASIC CONSIDERATIONS

The chief interest in this text is in the field of subclinical coronary heart disease, that is the period when accumulation of

risk of future clinical coronary heart disease goes on silently, undoubtedly via the mechanism of progressive narrowing of the coronary arteries. It is, therefore, important to avoid confusing this phase of coronary heart disease with *extremis* phases of clinical coronary heart disease, such as angina decubitus. Thus preventive or therapeutic considerations that may apply to the person in the subclinical phase of coronary heart disease, either before the first clinical episode or during the interim period between clinical episodes, may not apply to the patient with severe angina pectoris or cardiac decompensation. This differentiation is commonly missed in much of the medical literature on the subject of thyroid and coronary heart disease. Let us suppose it has been demonstrated that administration of desiccated thyroid substance may intensify angina pectoris in some patients who already have angina pectoris This *need not necessarily* have any bearing whatever upon the question of utilization of desiccated thyroid substance (and related agents) for purposes of achieving and maintaining lowered lipoprotein levels and Atherogenic Index values in persons free of clinical manifestations of coronary heart disease

THE BLOOD LIPOPROTEINS AND ATHEROGENIC INDEX IN SPONTANEOUS MYXEDEMA AND INDUCED HYPOTHYROIDISM

The extremely high incidence of elevation in the blood cholesterol level both in spontaneous myxedema and in induced hypothyroidism have long been known to physicians. In recent years, with the availability of modern physico-chemical techniques it has been possible to identify the intimate nature of the blood lipid disturbance both in spontaneous and in induced hypothyroidism and myxedema. The lipoprotein findings for untreated spontaneous myxedema are illustrated below for two typical cases

	S_f0-12 (mg/100ml)	S_f12-20 (mg/100ml)	S_f20-100 (mg/100ml)	S_f100-400 (mg/100ml)	Atherogenic Index (Units)
Case 1 44 year old woman	750	130	112	18	119
Case 2 60 year old woman	827	195	103	16	157

The major features of importance are the massive elevation in the S_f0-12 and S_f12-20 lipoproteins, the absence of any appreciable elevation in S_f20-100 and S_f100-400 lipoproteins, and the marked elevation of Atherogenic Index which results from the S_f0-12 and S_f12-20 lipoprotein elevation. The induction of hypothyroidism and myxedema by surgical means, by radioiodine, or by pharmaceutical agents of the thiouracil type produces a *hypercholesterolemia* of the same form, namely an elevation of S_f0-12 and S_f12-20 lipoprotein levels above the corresponding pre-treatment levels. Therapy of myxedema with desiccated thyroid substance, thyroxine, or tri-iodothyronine results in a reduction in level of the S_f0-12 and S_f12-20 lipoproteins.

The marked elevation of S_f0-12 and S_f12-20 lipoprotein levels and hence, the Atherogenic Index, in either spontaneous or induced myxedema would be expected to lead to an accelerated rate of development of subclinical coronary heart disease and, therefore, to a high risk of future clinical manifestations There exists no reason, on a priori grounds, to assume that Atherogenic Index elevation resulting from myxedema should behave any differently with respect to increasing coronary heart *disease risk than would elevation for any other reason.* Physicochemically and chemically the lipoproteins of the S_f0-12 and S_f12-20 classes, which become elevated in myxedema, are similar to those which occur in health and in a variety of other diseases. There is no reason why the risk tables of Chapter V should not be used in the case where lipoprotein elevation is produced by myxedema Yet there is current, in some quarters, the idea that the elevation in blood lipoproteins (or blood cholesterol) in hypothyroidism or myxedema is "safe," in that it neither accelerates coronary arteriosclerosis development nor increases the risk of clinical coronary heart disease. This idea is based upon inadequate evidence plus erroneous interpretation and analysis of what evidence does exist Blumgart and his co-workers[83] have sponsored the view that the blood lipid elevation in hypothyrodism and myxedema does not accelerate coronary arteriosclerosis Their evidence for this view deserves careful appraisal These workers have had experience with the therapeutic use of induced hypothyroidism for alleviation of intractable angina pectoris and

congestive heart failure. In a publication[53] dealing with eight patients who had survived one to thirteen years after surgical total thyroidectomy, Blumgart and co-workers drew the conclusion that "The results demonstrate that progressive atherosclerosis of the coronary arteries is not a necessary concomitant of increased blood cholesterol levels in hypothyroidism or of the hypothyroid state" This sweeping generalization would be important indeed if the evidence presented by Blumgart and associates could support it, but the evidence does not do so. The series of patients they reported included five men and three women.

For the five men, the following values are obtained from analysis of the data presented:

Mean age at thyroidectomy	34.0 years
Mean initial blood cholesterol level	197.0 mg/100ml
Mean duration of life in the myxedematous state	8.3 years
Mean blood cholesterol during the period of life in the myxedematous state	335.2 mg/100ml

For the three women, the following values are obtained.

Mean age at thyroidectomy	40.3 years
Mean initial blood cholesterol level	198.0 mg/100ml
Mean duration of life in the myxedematous state	6.2 years
Mean blood cholesterol level during the period of life in the myxedematous state	277.3 mg/100ml

Based upon gross, semi-quantitative evaluation of the post-mortem state of the coronary arteries, the conclusion was drawn that "the degree of involvement of the coronary arteries was certainly no greater and probably less than that generally witnessed in similar euthyroid individuals with the same disease process." No evidence was presented for such similar euthyroid individuals to facilitate this comparison. Among many questions that must be asked is, "Are these eight patients representative, in their initial state before myxedema induction, of euthyroid individuals?" The mean blood cholesterol initially for the five men was 197.0mg/100 ml. From data in the literature[54] the mean cholesterol level (by similar methods) for men of this age in the population at-large is 218.0 mg/100 ml. The mean blood cho-

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The marked elevation of S_f0-12 and S_f12-20 lipoprotein levels and hence, the Atherogenic Index, in either spontaneous or induced myxedema would be expected to lead to an accelerated rate of development of subclinical coronary heart disease *and, therefore, to a high risk of future clinical manifestations* There exists no reason, on a priori grounds, to assume that Atherogenic Index elevation resulting from myxedema should behave any differently with respect to increasing coronary heart disease risk than would elevation for any other reason. Physicochemically and chemically the lipoproteins of the S_f0-12 and S_f12-20 classes, which become elevated in myxedema, are similar to those which occur in health and in a variety of other diseases. There is no reason why the risk tables of Chapter V should not be used in the case where lipoprotein elevation is produced by myxedema Yet there is current, in some quarters, the idea that the elevation in blood lipoproteins (or blood cholesterol) in hypothyroidism or myxedema is "safe," in that it neither accelerates coronary arteriosclerosis development nor increases the risk of clinical coronary heart disease. This idea is based upon inadequate evidence plus erroneous interpretation and analysis of what evidence does exist Blumgart and his co-workers[83] have sponsored the view that the blood lipid elevation in hypothyrodism and myxedema does not accelerate coronary arteriosclerosis. Their evidence for this view deserves careful appraisal. These workers have had experience with the therapeutic use of induced hypothyroidism for alleviation of intractable angina pectoris and

matous average men would have accumulated by the age of 42.3 years, which is the age at which Blumgart's male patients died. As a result of the myxedema induction and the elevation of Atherogenic Index of 45 units resulting therefrom, those patients would have accumulated 45x8 3, or 374 units more than the average non-myxedematous man. Blumgart's males, therefore, at death would have accumulated a total of 2814 units (obtained by adding 374 to 2440) in comparison with 2440 units for non-myxedematous men at this age. Similar calculations are readily made for the women. The average non-myxedematous woman at 40 3 years has an Atherogenic Index of 55.5 units and by 46 5 years, an Atherogenic Index of 59.5 units. At 40 3 years, such a woman would have accumulated 1790 units. During the 6.2 years thereafter (corresponding to the myxedema period for Blumgart's female patients), average non-myxedematous women would accumulate (6 2) (57 5), or 357 additional units, giving a total accumulation of 1790 + 357, or 2147 units As a result of the myxedematous state, Blumgart's *three women* would have accumulated an extra 25x6 2, or 155 units Therefore, at 46 5 years, which is the age of death of Blumgart's *women*, they would have accumulated 2302 units in comparison with 2147 *units* expected for non-myxedematous women of the same age.

Elsewhere[73] it has been shown that the total accumulation (measured by Atherogenic Index multiplied by *time*) parallels extremely closely the quantitative changes in degree of coronary arteriosclerosis with age in the United States, wholly independent of any consideration of cause and effect relationships Therefore Blumgart could have expected his myxedematous men to have a 15 3% increase in degree of coronary arteriosclerosis compared with non-myxedematous men of the same age corresponding to the 15 3% greater accumulation calculated above. Similarly he could have expected a 7.2% increase in degree of coronary arteriosclerosis compared with non-myxedematous women of the same age, corresponding to the calculated 7.2% increase in accumulation due to the myxedema From the known extent of variation in degree of coronary arteriosclerosis in men of a particular age, or in women of a particular age, it can be estimated that to prove a 15.3% increase in degree of coro-

lesterol level initially for the three women was 198.0 mg/100 ml. For women of this age in the population-at-large the mean cholesterol level is 210 mg/100 ml. If blood cholesterol level is related to coronary arteriosclerosis development, it can be stated that the eight patients, *without* myxedema, should have showed an average, or slightly lower-than-average degree of coronary arteriosclerosis. The crucial issue at hand is how much would the period of life these patients experienced with some elevation of blood cholesterol have increased the expected degree of coronary arteriosclerosis above average?

This question can be answered utilizing the concept of accumulation of coronary arteriosclerosis. First, since the blood cholesterol elevation in myxedema is almost wholly in S_f0-12 and S_f12-20 lipoproteins, the extent of elevation of these lipoprotein classes can be calculated, since they are known from chemical data to contain 34% cholesterol by weight. Thus, for the five men in the series the mean elevation of blood cholesterol of 138.2 mg/100 ml above the initial value corresponds to an elevation of S_f0-20 lipoproteins of 138 2 over 0.34 or 407 mg/100ml. For the three women in the series the mean elevation of blood cholesterol of 79.3 mg/100 ml above the initial value corresponds to an elevation of S_f0-20 lipoproteins of 79.3 over 0.34 = 233 mg/100 ml. Since these lipoproteins inculde the S_f12-20, which receives a weighting of 1.75 times that of the S_f0-12 lipoproteins, the elevation in lipoproteins for the men corresponds to approximately a 45 unit increase in Atherogenic Index for the men and to a 25 unit increase in Atherogenic Index for the women. On the accumulative basis, where Atherogenic Index multiplied by time is considered (see Chapter VII), the average 34 year old man, whose Atherogenic Index is 68.6 units, will have accumulated 1834 units In the 8 3 year period (the length of time Blumgart's male patients were myxedematous; this average man would accumulate additional units Since by 42 3 years his Atherogenic Index, without myxedema induction, would be 77.3 units, the average Atherogenic Index for the 8.3 year period would have been 68.6 + 77.3 over 2, or 73.0 units. Therefore, the *additional* accumulation would have been 73.0x8.3, or 606 units. Adding 606 to 1834 gives 2440 units which non-myxede-

to the pre-therapy levels in spite of maintained administration of three grains of thyroid substance per day. This apparent "escape" phenomenon has a reasonable explanation. During the early period of administration of thyroid substance the patient has available the exogenously administered plus the endogenously produced thyroid hormone. As administration of exogenous hormone continues, endogenous thyroid hormone production is suppressed via the thyroid-thyrotropin system, until finally a point is reached where the *total* supply of thyroid available to the patient is not appreciably different from that available before the inception of administration of thyroid substance, except that it is by such a time largely exogenous rather than endogenous in source. A reasonable corollary of this explanation would be that in order to achieve maintained lipoprotein lowering by exogenous thyroid administration sufficient thyroid must be given so that even if complete shutdown of endogenous production of thyroid hormone occurs, there would still be more thyroid available to the patient than was available before the administration of the exogenous supply. From the long-term studies of Strisower and co-workers[85] it appears that with doses of 4 or 5 grains of U.S.P. desiccated thyroid substance per day such a point is reached for most persons within the usual ranges of lipoprotein distribution. With these doses the level of lipoproteins is lowered and is maintained lower without any evidence of an "escape" phenomenon. The magnitude of lowering of lipoprotein levels that were achieved with doses of 5 grains of desiccated thyroid substance per day is shown in the data of Table XLVI. There the 39 cases studied extensively by Strisower have been segregated into three separate groups, ranked according to initial level of the various lipoprotein classes. Thus not only is the effect of thyroid substance demonstrable, but its relationship with the initial lipoprotein status of the subject can be ascertained. Inspection of these data shows that with a dose of 5 grains of thyroid substance per day there occurs a sustained lowering in mean level of all four lipoprotein classes, S_f0-12, S_f12-20, S_f20-100, and S_f100-400 over the entire 36 week period of hormone administration. For any one of the four lipoprotein classes, the extent of reduction in lipoprotein level as a result of thyroid adm

nary arteriosclerosis among such male myxedema patients compared with non-myxedematous men would require careful quantitative assessment of degree of sclerosis in a series of about 100 myxedematous men and 100 non-myxedematous men of the same age. The demonstration of a 7.2% increase in coronary arteriosclerosis for the myxedematous women would require careful quantitative study of about 300 myxedematous women's coronary arteries and those of about 300 non-myxedematous women of the same age Yet by semi-quantitative grading Blumgart and his associates have made the decisions on five male patients and three female patients, respectively, without even presenting any data for matched non-myxedematous patients. The only conclusion reasonable in the light of these considerations is that the material studied by Blumgart and associates was entirely inadequate, and hence unsuitable, for attempting any answer to the question of the relationship of myxedema, hypercholesterolemia, and arteriosclerosis Certainly, their evidence should in no way even suggest the idea that the blood lipoprotein and Atherogenic Index elevation in patients with myxedema are of different meaning for coronary disease than they are in any other persons.

THE EFFECT OF DESICCATED THYROID SUBSTANCE UPON SERUM LIPOPROTEIN LEVELS AND ATHEROGENIC INDEX VALUES

Strisower and co-workers[79] have carried out extensive investigations of the effect of desiccated thyroid substance upon the various lipoprotein classes *Dosage* of thyroid substance is a highly critical factor in such studies, for depending upon dosage and time of blood sampling, *apparently* paradoxical results may be obtained. With a dose of one to two grains of desiccated thyroid substance daily in most euthyroid adults very little alteration in lipoprotein level is observed. With a dose of three grains per day from the start most euthyroid subjects experience an appreciable lowering of $S_f0\text{-}12$ and $S_f12\text{-}20$ lipoprotein levels during the first few weeks of administration of the thyroid Thereafter, there occurs, in most cases, a progressive rise in the levels of these lipoproteins completely, or almost completely, back

effect of administration of 5 grains per day of thyroid substance on the Atherogenic Index values for the 39 patients described above is presented in Table XLVII. The patients are ranked in that tabulation upon their initial, pre-thyroid Atherogenic Index values. It is evident that the group with very high Atherogenic Index values showed a very marked drop in Atherogenic Index value in response to continuous administration of desiccated thyroid substance. This is, of course, precisely the group that would clinically be considered to be in need of lowering of the Atherogenic Index value with respect to prophylaxis of future coronary heart disease.

In the discussion of familial factors in coronary heart disease (Chapter VI) the families characterized by massive elevation of S_f0-12 or S_f0-12 and S_f12-20 lipoprotein levels were described. These families show the same type of lipoprotein derangement which characterizes myxedema, although they show no clinical stigmata of myxedema. Such families, none-too-rare in the United States population, are known to have an inordinately high risk of clinical coronary heart disease for those members of the family who *do* inherit the lipoprotein abnormality. Both from the biochemical viewpoint and for possible practical prophylactic reasons the response of persons characterized by this particular

TABLE XLVII

EFFECT OF FIVE GRAINS OF DESICCATED THYROID SUBSTANCE PER DAY UPON ATHEROGENIC INDEX VALUES IN RELATION TO PRE-THERAPY ATHEROGENIC INDEX VALUES

Mean Initial Atherogenic Index (units)	*Mean Atherogenic Index After 36 weeks on 5 Grains of Desiccated Thyroid Daily (units)*	*Change in Mean Atherogenic Index (units)*
Overall Group of 39 Cases		
70.0	52.0	− 18.0
The 10 Cases with highest Initial A.I. Values		
94.1	64.0	− 30.1
The 19 Cases with intermediate A.I. Values		
71.5	53.1	− 18.4
The 10 Cases with lowest Initial A.I. Values		
45.0	37.1	− 5.9

TABLE XLVI

BLOOD LIPOPROTEIN RESPONSE TO DAILY ADMINISTRATION OF FIVE GRAINS OF DESICCATED U.S.P. THYROID SUBSTANCE IN RELATION TO PRE-THERAPY LIPOPROTEIN LEVELS

Range of Levels (mg/100ml)	*Mean Initial Lipoprotein Level*	*Number of Subjects*	*Lipoprotein Level after 36 weeks on 5 grains of thyroid daily (mg/100ml)*	*Change in Mean Lipoprotein Level (mg/100ml)*
S_f0-12 Lipoproteins				
Over 400	127	16	340	− 87
300-400	350	15	295	− 55
Below 300	218	8	184	− 34
S_f12-20 Lipoproteins				
Over 100	145	8	47	− 98
50-100	76	17	29	− 47
Below 50	37	14	23	− 14
S_f20-100 Lipoproteins				
Over 100	120	13	94	− 26
70-100	81	10	73	− 8
Below 70	54	16	54	0
S_f100-400 Lipoproteins				
Over 50	88	10	45	− 43
25-50	36	10	21	− 15
Below 25	16	19	13	− 3

in those individuals initially characterized by the highest levels of that particular lipoprotein class, is somewhat less for the initially intermediate group, and is least for the group with the lowest lipoprotein levels One possible interpretation of these findings is that individuals with the highest lipoprotein levels may be *relatively* deficient in thyroid hormone availability, even though on usual clinical grounds no evidence of frank hypothyroidism is present.

PRACTICAL CLINICAL IMPLICATIONS OF THE EFFECT OF EXOGENOUS THYROID SUBSTANCE UPON SERUM LIPOPROTEIN LEVELS

With respect to the potential application of the profound effect of desiccated thyroid subtance upon blood lipoproteins, it is of great interest to know how the overall Atherogenic Index value is affected by the administration of thyroid substance. The

TABLE XLVIII

RESPONSE OF PATIENTS WITH S_f0 20 HYPERLIPOPROTEINEMIA TO DESICCATED THYROID SUBSTANCE

Case No	Age & Sex	Initial Lipoprotein Levels S_f0 12	Initial Lipoprotein Levels S_f12 20	Initial Lipoprotein Levels S_f20 100	Initial Lipoprotein Levels S_f100 400	Atherogenic Index	Maximum Thyroid Dosage Reached and Duration of this Dosage*	Initial Body Weight (pounds)	Weight at time last sampling (on maximum thyroid dosage) (pounds)	Lipoprotein Levels at Time of Maximum Thyroid Dosage S_f0 12	Lipoprotein Levels at Time of Maximum Thyroid Dosage S_f12 20	Lipoprotein Levels at Time of Maximum Thyroid Dosage S_f20 100	Lipoprotein Levels at Time of Maximum Thyroid Dosage S_f100 400	Atherogenic Index	Total Duration of Thyroid Administration including period on maximum dosage**
1	48M	554	136	212	86	137	3 grs for 5 mo	195	198	180	122	170	56	109	9 months
2	22F	658	139	28	0	95	5 grs for 7 mo	105	111	571	10	14	1	73	19 months
3	5M	643	51	43	2	81	5 grs for 4 mo	10	44	155	32	31	6	58	12 months
4	30F	665	98	13	2	92	5 grs for 2 mo	133	136	518	59	62	15	79	12 months
5	40F	533	61	16	8	73	5 grs for 2 mo	156	152	362	36	57	19	56	11 months
6	11F	822	131	66	0	117	5 grs for 4 mo	71	88	161	76	93	31	81	21 months
7	33F	938	118	83	6	130	7 grs for 1 mo	115	114	629	66	82	35	95	21 months
8	8F	617	99	31	8	86	5 grs for 5 mo	81	86	395	44	31	9	55	14 months
9	10M	920	201	110	10	148	7 grs for 2 mo	180	155	660	135	138	50	123	11 months
10	11F	935	155	98	2	138	8 grs for 4 mo	131	147	588	98	112	23	100	14 months
11	5F	815	110	57	10	115	3 grs for 13 mo	51	59	508	13	22	6	63	24 months
12	19M	1075	167	133	20	161	4 grs for 3 mo	170	163	905	108	172	31	145	9 months
13	58F	888	175	218	79	177	4 grs for 2 mo	151	151	591	112	151	50	119	7 months
14	37M	826	117	151	76	143	2 grs for 2 mo	136	159	656	112	231	214	168	6 months
15	68F	1033	160	161	31	165	4 grs for 2 mo	166	164	701	133	129	50	125	7 months
16	19M	580	171	116	28	115	3 grs for 1 mo	189	177	431	103	127	30	89	13 months

* These studies are still in progress. The "maximum" thyroid dosage is simply that which has been reached at the time of this evaluation, and in no way implies maximum thyroid tolerance of the patient.

** In general the patients were started with a dosage of 1 grain of desiccated thyroid per day and the dose built up over varying periods thereafter, depending upon response.

familial hyperlipoproteinemia is of intense interest. Sixteen such subjects have been treated with desiccated thyroid substance for varying periods of time. The results achieved are presented in Table XLVIII. It is evident that such persons are distinctly capable of responding to administration of thyroid substance with a marked lowering in the level of S_f0-12 and S_f12-20 lipoprotein. Furthermore, many such responses occur without weight loss or even in the face of a net gain in weight. Clinical evidence of thyroid toxicity has been a rare occurrence in these subjects

The clinician reflecting upon these large effects of exogenous thyroid substance on serum lipoprotein levels and Atherogenic Index values will, in many instances, still be hesitant to consider the use of exogenous thyroid substance as a preventive measure in the sub-clinical phase of coronary heart disease. He will undoubtedly be mindful of the fact that caution is indicated in the rate of buildup of the dosage of thyroid substance in patients with myxedema, where too energetic thyroid replacement therapy has been reported to result in myocardial infarction The presumed mechanism in such cases is an increased caloric expenditure by the myocardium in the presence of an embarrassed coronary blood flow resulting from extensive coronary arteriosclerosis The clinician will also be mindful of the reports that angina pectoris can be exacerbated by the administration of thyroid-active agents and that intractable angina pectoris can be relieved in some cases by thyroid ablation. But the patient with frank and long-standing myxedema and the patient with intractable angina pectoris are hardly those upon whom the broad interest in possible use of thyroid substance to diminish the rate of progression of sub-clinical coronary heart disease is focussed Rather the persons of interest are relatively youthful individuals with massive elevation in lipoprotein levels and Atherogenic Index values. The outlook for such persons is gloomy unless their lipoprotein status can be improved and maintained so for long periods of time. Some such subjects will show minor calorigenic effects of exogenous thyroid substance; others will not. Careful clinical observation of these persons during administration of thyroid substance is essential. Biochemistry, biophysics, and mathematics can aid

Chapter XIV

OCCUPATION, STRESS, PHYSICAL EXERCISE, AND CORONARY HEART DISEASE

It is not the need of a chapter in this book in which to place "residual" material that leads to the grouping of occupation, stress, and physical exercise together in the discussion of each in relationship with coronary heart disease. Rather, this grouping results from the observations (to be detailed below) showing that occupation is in some way related to coronary heart disease and from the emphasis placed by some investigators either upon stress or physical exercise as the factors accounting for the occupational differences in incidence rate of coronary heart disease. Unfortunately, this area is considerably beclouded by semantic difficulties, by emotionalism, by pre-conceived concepts, and by inadequate quantitative data. Yet it is an important area, for every physician faces daily questions referable to this area from his patients with coronary heart disease and from those who would like to avoid that disease

Semantic and measurement difficulties surround one of these factors especially, namely stress Definitions of emotional, occupational and life stresses are nearly as frequent as are investigators of the problem Qualitative impressions are rife. Many are certain that the *pace of modern living* create stresses upon man never before equalled in history, although even semi-quantitative evidence to support this statement has not yet been forthcoming Such workers point to the apparently real rising incidence of clinical coronary heart disease in Western countries over the past several decades and to the pace of living in these regions over the same time period. Then they state flatly that it is obvious that the stress is clearly the basis for the increase in

clinical medicine, but they are hardly intended to be a replacement for seasoned clinical judgment. If calorigenic effects should develop and should be deemed clinically dangerous, then these particular persons probably cannot take advantage of the lipoprotein-lowering effect of thyroid substance. Most persons receiving thyroid substance will not show calorigenic effects sufficient to warrant discontinuation of thyroid administration.

There have recently been reported a few cases receiving tetraiodothyroacetic acid[86] where lowering of blood lipids was achieved without appreciable alteration of the basal metabolic rate or other evidence of calorigenic effects. This has raised hopes[87] that a pharmaceutical agent might be at hand which might provide the desirable effect upon blood lipoprotein levels while averting the unwanted possible calorigenic action. However, *these studies were not controlled by comparison* of the effects of desiccated thyroid substance on the same patients, a highly necessary control. Strisower and co-workers showed that many patients in their series exhibited no evidence of appreciable calorigenic action, such as weight loss, or such effects as pulse rate increase, but still showed marked lowering of lipoprotein levels. Nevertheless, inasmuch as the remarkable effect of thyroid-active substances upon blood lipoproteins has not been proved to be part of the calorigenic action of such agents, pharmacologic studies directed toward achievement of derivatives which may dissociate these effects appear worthwhile.

lying evidence may perhaps be somewhat stronger than critical evaluation would reveal it to be

OCCUPATION AND CORONARY HEART DISEASE

Consideration of this overall area may logically start with evaluations of occupation in relation to coronary heart disease, for occupational "stresses" have been indicted by many as a major predisposing factor in coronary heart disease. There do exist some factual data concerning the incidence rate of coronary heart disease in various occupational categories. Morris[88] has been especially active in the evaluation and presentation of data pertinent to occupational incidence rate of clinical coronary heart disease His studies indicating a higher frequency of clinical coronary heart disease and a more severe form of coronary heart disease in the drivers of double-decker London buses compared with the conductors of such buses are now classic in the medical literature. He has, further, provided data summarizing the incidence rate of clinical coronary heart disease in a wide variety of occupational categories for Great Britain. These occupational groups and their coronary heart disease incidence rates are listed in Table XLIX There is every reason to consider that occupational differences of appreciable magnitude *do* exist in the incidence rate of clinical coronary heart disease, well above any attributable to statistical sampling errors. It is, rather, the step beyond this conclusion which is so difficult. *Why do* occupational differences in incidence rate of clinical coronary heart disease exist? Morris recognized the difficulties involved in interpretation of the occupational differences in coronary heart disease and especially that no one ready explanation would be considered to explain all the observations Among the major possibilities that have received consideration are (1) The type of person who, in general, makes the choice of a particular occupation, or has it effectively made for him by circumstances, may differ in many ways from the type of person in some other occupation Physical habitus, muscularity, intellect, temperament, background and a host of other factors could well help determine who is to be found in a particular occupation. Should this be the major basis

incidence rate of clinical coronary heart disease. Yet no such conclusion seems obvious to the critical observer who places some reliance upon quantitative methods in modern medical science. It has been pointed out previously (Chapter XIII) that the quantitative disciplines do not in any way invalidate the continuing necessity for clinical judgment in medicine, but on the other hand this statement does not imply that unbridled impression can serve as evidence in lieu of quantitative measurement.

The essence of the difficulty with the evaluation of stress as a potential factor in coronary heart disease lies in the variability of its definition and the almost complete absence of satisfactory methods for its measurement, even on a crude, semi-quantitative basis This necessarily makes any reasonable evaluation of its possible significance difficult, at a minimum. One finds it unsatisfactory to accept quantitation in terms of stressful situations, personal, social, economic, or other inasmuch as what really is of concern is the effect of any particular stressful situation upon a particular individual. A set of circumstances mildly stressful to one person can readily be conceived to be either mildly, moderately, or overwhelmingly stressful to some other person Hence, what is needed is some method of quantitating the nature of the interaction of the situation with the individual and the extent of effect of such interaction upon that individual Even if such a method were of semi-quantitative character, but objectively executed, involving a grading of stress on a scale of plus one to plus four, enormous progress could then be made in the evaluation of any possible relationship of stress in humans with the evolution of coronary heart disease. But no such method has been described, and worse yet, most evaluations to date have involved retrospective evaluation of the stress, once the biochemical or clinical alterations of interest had already been observed, a procedure fraught with massive danger of bias. Nevertheless, it is of some merit to examine what evidence has been brought forward purporting to relate stress to coronary heart disease in man Especially is this important to do since some of the advocates of the stress concept are rather positive in their assertions, leaving the impression that the under-

require identification and a determination of whether or not *new*, or *independent*, information is provided with respect to coronary heart disease. This point deserves amplification. Suppose that the circumstances of a particular occupation were such as to modify significantly the dietary habits of persons in that occupation, either as a result of location, availability of certain foods, or social circumstances within the occupation. It would be possible that animal sources of fat, for example, might be increased in the habitual diet. From previous considerations (Chapter X) it would be predicted that this dietary alteration would provoke an elevation of the S_f0-12 and S_f12-20 lipoproteins, and through this, the Atherogenic Index would be elevated, and would hence lead to an increase in expected incidence rate of coronary heart disease for the occupational category itself. But this would really not be new, or independent information concerning factors involved in the evolution of coronary heart disease, for it would have reduced itself to one of the two known basic factors, namely blood lipoproteins and blood pressure level. To be sure it would be important to identify the fact of a habitual alteration in diet being a basis for an occupational predisposition to coronary disease, but this would be a discovery of minor magnitude in comparison with adding an additional basic factor to the two which are known.

(2) The many and varied stressful features of certain occupations have been considered by Morris and others as a possible basis for observed differences in coronary disease incidence rates. Morris concluded that, considering all the occupational groups involved, it would be difficult to frame a hypothesis built around stress of the occupation that would be satisfactory to explain the findings. Others have quickly pointed to the differences between the stressful factors in the occupational life of a bus driver in congested London traffic in comparison with the presumed lesser stresses in that of the conductor of the double-decker bus. Whether the bus driving in congested traffic is stressful or relaxing to a London bus driver is not as simply decided as some would make it seem. Much depends upon the reaction of the type of man who is a bus driver in the evaluation of what stress he experiences in his occupation. Even if it were conceded that bus

TABLE XLIX

DEATH RATE FROM CORONARY HEART DISEASE IN RELATION TO OCCUPATION
(45-64 YEAR OLD MEN
ENGLAND, AFTER MORRIS)

Occupational Category	*Death Rate from Coronary Heart Disease (number per million per year)*
Hairdressers, etc.	880
Makers of Textile Goods	770
Typists and other Clerks (Non-Civil Service)	730
Fitters, Mechanics, Tool Makers, etc.	560
Messengers and Porters, etc.	500
Railway Engine Drivers	*480*
Postmen and Sorters	460
Boot and Shoe Makers, Repairers	450
Smiths and Skilled Forge Makers	420
Metal Machinists	380
Coal Hewers and Getters	290
Water Transport Dock Laborers	270
Coal Mine Workers below ground, except Hewers and Getters	230
Other Workers in Building, etc.	170
Agricultural Gardeners, Laborers, etc.	150

for the differences in occupational incidence of coronary heart disease, the problem would reduce itself to that of understanding what features of particular types of persons account for an inordinate susceptibility to coronary heart disease. Illustratively, if obese men should represent a much higher proportion of those engaged in one occupation versus others, that occupation would be expected to show a higher incidence rate of coronary heart disease than the others because obesity is definitely known to increase the risk of such disease (See Chapter IX) This would be true even if no features of the occupation or the interaction of the individual with his occupational environment existed. On the other hand it could be that persons of a particular type might tend to select a certain occupation, and that the interaction of the occupational environment with that particular type of individual might lay the groundwork for future manifest coronary heart disease. In such an event that interaction would

id blood pressure, or whether it provides a third factor of *ndependent* importance in coronary heart disease. Occupational udies, including the physical activity factor, are unquestionably eeded to provide some of the critical answers.

RELATIONSHIP OF OCCUPATION WITH FACTORS KNOWN TO BE OF IMPORTANCE IN CORONARY HEART DISEASE

(a) Blood Lipoproteins, Atherogenic Index and Occupation

Several years ago the author and his colleagues undertook some long-range studies of the various characteristics of the human population which influence habitual distribution of blood lipoproteins. With the already-available knowledge that even for a specific age and sex group, considerable variability still characterizes the population with respect to blood level of such lipoproteins as the S_f0-12, S_f12-20, S_f20-100, and S_f100-400 classes, it seemed extremely worthwhile to make a continuing effort to ferret out possible bases for such variability. Further, serial study of population groups allows for the possibility of understanding some of the sources of variability of lipoprotein level within individual subjects. Occupational category was considered as one major variable of importance for study. Since it was desirable to eliminate certain types of extraneous sources of possible variation, the decision was made to study subjects in one industry, working and residing in one general locale. In this way, such possible sources of variation as climatic, geographic, and general features of the occupational environment are greatly minimized. Of course, the persons who work in one industry do have a previous background of differing geographic contacts, of having been in other industrial locations, and other features that render them heterogeneous. Nevertheless the common environment they share at the time of study which for most of them was over one year after they had been employed in this single industrial area would have tended to decrease heterogeneity in as practical a way as is possible for such studies. In this industry* a reasonable distribu-

*University of California Radiation Laboratory at Livermore, California (Employees number approximately 2500)

driving were more stressful than conducting, there remain numerous other pairs of occupations, differing in coronary disease incidence rates, where such possible stress differences are not so apparent. For example, clerks in England have a higher coronary heart disease rate than postmen. Assessment of stress factors for these two groups is not immediately obvious. Unfortunately many who have assigned stress ratings to occupational groups have done so *retrospectively*, once it was known which occupational group had the higher incidence rate of coronary heart disease. It is regrettable that no more objective and quantitative approach to stress evaluation is available to replace the highly subjective, retrospective one.

(3) *Physical Activity in Occupations:* Morris felt that his own evidence as a whole pointed most strongly to physical activity of the occupation as the feature of prime importance in determination of the incidence of coronary heart disease for the occupation. Thus the bus drivers in London double deckers, *seated* in their occupational activity for some eight hours of every working day, do have far less activity *at work* than the conductors, who make numerous trips up and down the bus stairs daily. Upon review of the other occupational categories, Morris found a reasonable inverse relationship between the physical activity of the occupation and the incidence rate of clinical coronary heart disease This inverse relationship appears, from Morris' data to be well-established The important question which follows is "How does it operate?" Does physical activity at work of and by itself really provide some degree of protection against coronary heart disease? If it does, would advocacy of physical exercise for those in more sedentary occupations be indicated in the effort to minimize their risk of coronary heart disease? These are points of enormous practical clinical consequence. Clearly it would be essential to learn whether the physical activity *per se* of certain occupations is the essential feature, or whether this is a reflection of some other feature, known or unknown If physical activity *is* important, it must operate by some definable mechanism. In approaching this issue of mechanism, it would be important to determine whether physical exercise (if it be a factor) in any way influences the two major known factors, blood lipoproteins

and blood pressure, or whether it provides a third factor of *independent* importance in coronary heart disease. Occupational studies, including the physical activity factor, are unquestionably needed to provide some of the critical answers.

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tion of occupations is represented, including unskilled labor, highly skilled labor, clerical, professional, scientific, and executive groups.

In all twenty-nine occupational listings, obtained from the personnel department records, characterized the individuals from this population sample under study. All subjects had periodic complete medical examinations at intervals of eighteen months, at which time the lipoprotein analyses were made. It is understood that at times a particular personnel listing, e.g., engineer, can mean work loads differing appreciably within the category from individual to individual. Thus the physical activity at work for each engineer can hardly be expected to be identical, but it was not deemed feasible to sub-categorize so extensively as to arrive at a great multplicity of sub-groups each containing so few individuals as to make analysis of the findings impossible. Therefore each of the twenty-nine occupational groups was kept together as a single entity. The age for each group was not identical, ranging plus or minus approximately five years on either side of 35.0 years of age. For comparison of lipoprotein levels in one occupational category with another, the small correction of the lipoprotein level for each category to what it would be at 35.0 years was made. Such small corrections are extremely good, since the age trend for each lipoprotein class is very well established (Table XXIV). The data for all twenty-nine occupational categories are presented in Table L. The range of mean Atherogenic Index values for the various occupational categories is truly startling. Excluding some of the categories where limited numbers of subjects were available for study, some of the differences observed are obviously real and of major magnitude For example, the series of fifty custodians show the low mean Atherogenic Index of 60.6 units which may be compared with the overall group of *all* occupations for which the mean Atherogenic Index is 69.1 units. The difference of 8.5 Atherogenic Index units is so large that sampling errors alone would lead to this large a difference about once in one hundred times. (See Table L for method of proving this In this case SE = 3 5, t = 2.4) Similarly, comparison of one of the categories showing a very high value, e.g., tool and die makers with a mean Atherogenic Index

TABLE L.

Atherogenic Index Values in Twenty Nine Occupational Categories in One Industry (Male Subjects)

(Ranked from Highest Atherogenic Index Values to Lowest)*

Occupational Category	*Number of Men*	*Mean Age (years)*	*Atherogenic Index (adjusted to 35.0 years) (units)*
Computer and Duplicating Machine Operators	21	31.1	79.6
Truck and Bus Drivers	24	33.6	79.4
Buyers	11	38.0	77.8
Tool and Die Makers	62	36.0	77.7
Mathematicians	61	28.3	75.9
Laboratory Technicians	47	31.5	75.8
Journeyman Machinists	77	36.9	75.6
Firemen	19	36.5	72.3
Painters	17	41.2	72.2
Mechanical Technicians	90	34.8	71.7
Carpenters	21	35.4	71.4
Welders	14	39.4	70.6
Riggers and Equipment Movers	10	36.3	69.7
Electricians	43	36.7	69.7
Engineers	276	35.4	69.6
Physicists	227	30.6	69.4
Draftsmen	110	33.1	69.2
Executives (Assistant and Junior Classifications)	68	36.3	68.6
Steam Fitters and Boiler Operators	21	43.2	68.3
Clerks	23	32.3	67.8
Electronic Technicians	170	32.6	67.8
Chemists	77	31.2	67.6
Machinists and Machinists' Helpers	74	37.4	66.7
Police Officers	105	41.4	65.9
Accelerator Operators	70	31.4	63.1
Storekeepers	30	35.2	62.8
Laborers	40	39.9	61.4
Custodians	50	49.1	60.6
Sheet Metal Workers	22	43.2	55.2
Overall Group (All Occupations)	1885		69.1

* Standard Deviation of the Atherogenic Index for the overall group is approximately 25 units. Therefore to test whether the mean for any occupational group is significantly different, the t test can be applied. The standard error is SE = 25 / ——,

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value of 77.7 units with a category with a low mean Atherogenic Index value, e.g. custodians with a mean Atherogenic Index value of 60.6 units reveals that there is less than one chance in 1000 *that so large a difference could arise by sampling alone. The conclusion* is safe that the difference observed is real.

It is of major consequence that real and *large* differences in *mean Atherogenic Index* values exist between men in various occupational categories. An estimate of the meaning of some of the differences observed is readily made by reference to Table XV. Thus, since differences such as those between values of 75 and 60 Athrogenic Index units have been shown to exist, incidence rates of coronary heart disease can be expected to differ by a factor of 4.97 over 2.59, or 1.9 *times* on the basis of the Atherogenic Index alone! Therefore, some insight is available as to part, at least, of the basis for occupational differences in incidence rate of coronary heart disease. What is of importance to determine is *why* some occupational categories should show different Atherogenic Index values from others Such features as the type of person who enters the occupation, the relative weights of the individuals, their smoking habits, and their dietary habits, deserve evaluation since such features have been shown to be of consequence with respect to Atherogenic Index values. The relative weights and the cigarette smoking habits for the men in the various occupational categories of Table L are available. since their weights were measured and they had been questioned concerning cigarette smoking during the examination. These data are presented in Table LI for each of the occupational categories Also in this table the combined mean value for all occupations characterized by Atherogenic Index values above the overall mean *and the combined mean value for all occupations with* Atherogenic Index values below the overall mean is presented Neither for relative weight nor for cigarette smoking can it be demonstrated that those occupations with high Atherogenic Index values are different from those occupations with low Atherogenic Index values Therefore it is clear that the broad features of the difference in Atherogenic Index with occupational categories cannot be explained either from differences in weight of the individuals or from differences in cigarette smoking habit

TABLE LI

Relative Weights and Cigarette Smoking Habits in Occupational Categories Ranked Upon Atherogenic Index

Occupational Category	*Number of Men*	*Mean Atherogenic Index (units)*	*Mean Relative Weight*	*Mean Number of Cigarettes Smoked Per Day*
Computer and Duplicating Machine Operators	21	79.6	1.08	10.7
Truck and Bus Drivers	21	79.4	1.06	8.7
Buyers	11	77.8	1.13	15.4
Tool and Die Makers	62	77.7	1.05	11.9
Mathematicians	61	73.9	0.99	8.0
Laboratory Technicians	47	73.8	1.02	11.4
Journeymen Machinists	77	73.6	1.05	9.2
Firemen	19	72.3	1.16	20.1
Painters	17	72.2	1.02	16.1
Mechanical Technicians	90	71.7	1.05	12.1
Carpenters	21	71.4	1.06	10.9
Welders	14	70.6	1.06	8.3
Riggers and Equipment Movers	10	69.7	1.07	10.5
Electricians	43	69.7	1.06	13.3
Engineers	276	69.6	1.05	8.9
Physicists	227	69.4	1.02	5.5
Draftsmen	110	69.2	1.02	9.4
Executives (Assistant and Junior Classifications)	68	68.6	1.05	15.9
Steamfitters and Boiler Operators	21	68.5	1.07	6.9
Clerks	23	67.8	1.00	13.4
Electronic Technicians	170	67.8	1.03	9.8
Chemists	77	67.6	1.05	7.1
Machinists	74	66.7	1.03	10.5
Police Officers	105	65.9	1.08	15.3
Accelerator Operators	70	63.1	1.01	8.9
Storekeepers	30	62.8	1.02	10.1
Laborers	40	61.4	1.07	12.0
Custodians	50	60.6	1.08	9.0
Sheet Metal Workers	22	55.2	1.04	12.7
All Occupations with Atherogenic Index Means Above 69.1 (the overall mean)	1133	71.4	1.041	9.4
All Occupations with Atherogenic Index Means Below 69.1 (the overall mean)	750	65.7	1.015	10.9

The failure of difference in body weight to explain the Atherogenic Index difference with occupation does not rule out the possibility that fatness may be important in this connection. The relative weight determination does not, of course, distin-

guish body weight made up of fat from that made of muscle, for example. It would still be possible that whereas the occupations characterized by low Atherogenic Index values do not show lower body weights, they might still represent individuals with less body fat and more muscle than the occupations with high Atherogenic Index values. This brings us to the question of the physical activity associated with various occupations. Four of the occupations with the lowest mean Atherogenic Index values, the laborers, the custodians, the accelerator operators and the storekeepers, are all characterized by extensive physical activity at work. *The four occupations with the highest mean Atherogenic* Index values, the computer and duplicating machine operators, the truck and bus drivers, the buyers, and the tool and die makers are certainly characterized by much less physical activity at work. It is not as readily apparent, however, that the occupations with an intermediate mean Atherogenic Index value are characterized by an intermediate degree of physical activity at work. However, other factors may in part operate here too. For example, the physicists do smoke significantly fewer cigarettes than the group as a whole, which will to some extent alter their position on the Atherogenic Index scale. Also, it must be remembered that, if physical activity *is* a major factor, possible differences in physical activity *outside* of work must also be considered Certain tests of the physical activity explanation do not, superficially at least, seem to provide consistency Thus physicists can be divided into two groups, the theoretical physicists and the experimentalists. It would be expected, on the average, that the experimental physicists have a greater degree of physical activity in their occupation than do the theorists. Yet the 45 theoretical physicists in the overall group of physicists showed an average Atherogenic Index of 65.1 units, whereas the 182 experimental physicists showed an average Atherogenic Index of 70 5 units. This is in the opposite direction from the expectations based upon physical activity of occupation alone as the basis for the observations

In the main, it does appear that the data concerning Atherogenic Index values for various occupations is consistent with the concept that physical activity at work is an important determinant, but that in selected groups other factors may operate to distort

this relationship. The findings are also, in the main, *consistent* with Morris' hypothesis that the physical activity of certain occupations is a protective factor against development of clinical coronary heart disease. The observations of a relationship between occupations and Atherogenic Index values need extensive broadening and understanding, for this area may provide a major clue to understanding one basis for the relationship of occupation with incidence rate of coronary heart disease.

TABLE LII

DIASTOLIC BLOOD PRESSURES IN TWENTY-NINE OCCUPATIONAL CATEGORIES IN ONE INDUSTRY

Occupational Category	*Number of Men*	*Mean Age (years)*	*Diastolic Blood Pressure in mm Hg (adjusted to 35.0 years)*
Painters	17	41.2	79.7
Firemen	19	36.5	73.6
Carpenters	21	35.4	73.1
Machinists and Machinists Helpers	74	37.4	72.9
Clerks	23	32.3	72.9
Tool and Die Makers	62	36.0	72.1
Custodians	50	49.1	71.5
Draftsmen	110	33.1	71.4
Journeyman Machinists	77	36.9	71.4
Truck and Bus Drivers	24	33.6	71.4
Electronic Technicians	170	32.6	71.3
Mathematicians	61	28.3	71.3
Storekeepers	30	35.2	71.3
Computer and Duplicating Machine Operators	24	31.1	71.2
Chemists	77	31.2	71.0
Physicists	227	30.6	70.9
Steamfitters and Boiler Operators	21	43.2	70.9
Engineers	276	35.4	70.9
Mechanical Technicians	90	34.8	70.5
Accelerator Operators	70	34.4	70.4
Police Officers	105	41.4	70.3
Executives (Junior and Assistant Classifications)	68	36.3	70.2
Buyers	11	38.0	70.2
Electricians	43	36.7	69.8
Laboratory Technicians	47	31.5	69.5
Laborers	40	39.9	69.1
Sheet Metal Workers	22	43.2	68.5
Riggers and Equipment Movers	10	36.3	68.1
Welders	14	39.4	66.3

(b) Diastolic Blood Pressure and Occupation

The diastolic blood pressures were routinely measured for the same group of 1883 men whose Atherogenic Index values were determined. The mean diastolic blood pressures, adjusted for the small age differences to an age of 35.0 years, are presented in Table LII. The only outstandingly high occupational group on the diastolic blood pressure scale are the painters. Statistical test indicates that there is less than one chance in one hundred that the extent of elevation observed would arise by sampling alone No other single occupational category can be proved to show diastolic blood pressures higher than the group as a whole. On the low side no single occupational category can be proved to show diastolic blood pressures different from the group as a whole. In general the means of the diastolic blood pressure show less spread than the means of the Atherogenic Index values for the different occupational categories. It does not appear, therefore, that variation of blood pressure with occupational category can help appreciably to account for variation in incidence rate of coronary heart disease. However, the pressures recorded here are taken after reclining 10 minutes. It cannot be stated, therefore, that members of certain occupational categories do not show episodic diastolic blood pressure elevations of consequence, even though their sustained diastolic pressures are not unusual.

OCCUPATIONAL "STRESS" AND ATHEROGENIC INDEX VALUES

Several recent publications[89, 90, 91] have referred to effects of emotional and occupational stress upon blood lipid levels. The occupational categories described above have been subjected to preliminary analysis, difficult as evaluation is in this area, for effects of such factors as job responsibility and demands upon Atherogenic Index values. From all the occupational categories together, those individuals were selected out who are listed on personnel records as supervisors, foremen, and coordinators, all of which are positions of special responsibility The mean Atherogenic Index for the entire group of 62 such men was found to be

68.6 units, contrasted with 69.1 units for the overall group of 1883 men. There is, therefore, no suggestion here that responsibility positions are characterized by any features that tend to elevate blood lipid values. As another test of the effect of responsibility of position, the entire group of engineers (one of the largest single categories available for analysis) was divided into subgroups based upon their official professional ratings. Higher professional ratings are accompanied by increased responsibility, increased demands, and a higher income. After adjustment of the Atherogenic Index values to 35.0 years of age for all the professional rating groups (since the higher rating groups were slightly older than those of lower rating), no significant difference was found to exist between engineers with the lowest professional ratings, for those with intermediary ratings, or for those with the highest professional ratings. If such factors as responsibility, demands, and frustration are really of consequence with respect to blood lipid levels, then it appears clear that currently reasonable approaches to measuring such stress features are inadequate to allow for discerning effects.

THE DIETARY BASIS FOR SO-CALLED OCCUPATIONAL "STRESS" EFFECTS

Friedman, Rosenman, and Carroll have recently reported[91] on changes in the serum cholesterol level purported to be the result of cyclic occupational stress in accountants, a stress they referred to as "socioeconomic stress." This stress was described by them as "a particular and rather specific type of emotional activity, namely that concerned with excessive "drive," competition, meeting "*deadlines*," and economic frustration." They were trying to study a form of stress further described by them as one which imposed a "sense of urgency" upon the subjects. It is of interest to note the basis upon which these authors selected this particular form of *stress*. Having convinced themselves that socioeconomic stress was correlated with the incidence of clinical coronary heart disease, they wanted to find out what kind of socioeconomic stress might be of importance. They therefore interviewed, by questionnaire, 162 executives of a large oil com-

pany, a railroad company, and 3 advertising agencies plus 47 physicians "actually treating cardiac patients." Since approximately 70% of both the lay and professional group chose the description of "socioeconomic stress" alluded to above, these investigators felt this must be the type worthy of study with respect to pathogenesis of clinical coronary heart disease. While this is a novel technique for deciding the probable etiology of disease, it is of interest to examine critically the far-reaching conclusions arrived at by these workers, for even accidental approaches to many problems have often led to highly important findings. Accountants were chosen as subjects because there existed, according to these investigators, a socioeconomic stress in these men predictably phasic enough during the first 5 months of the calendar year to allow periods of respite for control observation.

The period from April 2 to April 15 was considered by Friedman and co-workers to represent "severe stress," whereas May 14 to May 21 a period of "maximal respite" from stress In all, 39 accountants participated in the study throughout the entire period. From the data presented by these workers the following are the mean serum cholesterol levels for "Maximal occupational stress" and for "maximal respite";

During "Maximal Occupational Stress," Mean Cholesterol =	230 mg/100ml
During "Maximal Respite," Mean Cholesterol =	222 mg/100ml
Difference	8 mg/100ml

In order to evaluate whether or not dietary changes during these periods might have accounted for the serum cholesterol difference shown above, these workers took a very detailed dietary history for the two critical periods, April 2-9 ("maximal stress") and May 14-21 ("maximal respite"). Since so much reliance is placed upon these dietary records by the authors, our first approach must be to accept the dietary evaluations at face value and to determine whether they support the conclusion arrived at that stress itself, rather than dietary changes, was responsible for the observation of a change in mean cholesterol level of 8 mg/100ml The accountants were divided into two groups, depending upon the type of accounting they did Dietary evaluations were presented by Friedman and associates for

"maximal respite," and "maximal stress." The mean number of calories taken in daily for the combined group of 39 accountants during "maximal stress" was 1845 calories, whereas during "maximal respite" it was 1783 calories. Therefore, at face value, the accountants ingested 63 fewer calories per day during "maximal respite" then they did during "maximal stress." This caloric difference the investigators stated could not possibly have accounted for the 8 mg/100ml change in serum cholesterol upon which their thesis tests. Is this true? Friedman and associates made no effort whatever to test whether this caloric change could or could not explain the 8 mg/100ml change in cholesterol level. Instead they simply stated that it could not. But there do exist ample dietary data to test this issue quantitatively.

In the discussion of overweight and alterations of overweight, a "natural" experiment was described in which 374 subjects were studied twice at approximately one and one half year intervals. Those who lost weight showed lowering of s_f0-12, s_f12-20, s_f20-100, and s_f100-400 lipoprotein levels, whereas those who gained weight, showed increases in the levels of all these lipoproteins. Those who did not change in weight did not change significantly in lipoproteins. Taking all those data together, we have the following straight-forward estimations,

For 1 pound of weight loss in a time interval *of* 62.4 weeks,
the mean fall in s_f0-12 lipoprotein level = 1.5 mg
the mean fall in s_f12-20 lipoprotein level = 0.4 mg
the mean fall in s_f20-100 lipoprotein level = 1.7 mg
the mean fall in s_f100-400 lipoprotein level = 2.1 mg

In that observation period, subjects were gaining or losing weight at various rates, some over the entire 62.4 week interval, others, undoubtedly, over a small fraction of that interval. Most of the subjects did not even know their weight was changing. The *average* rate of caloric restriction to lose one pound of weight in 62.4 weeks is estimated as follows. Allowing for some water in body fat, it requires a restriction of approximately 4000 calories to lose one pound of weight. If this is to be lost, on the average, in 62.4 weeks, *the daily caloric* restriction must be 4000 over 62.4x7 or 9.2 calories per day. This number of calories restricted per day must, therefore, account for the falls in

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Indeed the dietary changes could readily have accounted for twice the observed changes. In summary, therefore, the conclusion of Friedman and associates that "the present studies indicate an extreme sensitivity of the serum cholesterol to the occurrence of emotional duress described as *socioeconomic stress*" might much better be replaced with the conclusion that accountants eat a little more when they are working long hours and that possibly their cholesterol levels rise a little during such times, in an amount expected from the extent of their dietary change.

What other observations are in the literature which claim to relate stress with serum cholesterol or other lipid levels are no more convincing than those just discussed. No critical evaluation of the quantitative changes observed and the extent to which they can be explained by concomitant dietary alteration is generally presented Thus the singling out of a few persons from a large group who show an appreciable change of serum cholesterol or lipoprotein level during an episode of presumed stress may very well reflect the singling out of the persons from the overall group who are most sensitive to relatively small dietary changes, since it is well known that such persons exist.

No acceptable evidence has yet been presented to suggest an effect of stress upon serum lipoproteins or serum cholesterol levels in man that cannot be as well, or better, explained by the solidly-established effects of dietary alterations upon such blood lipids It is to be hoped that some evaluation of the possible factor of stress will be made in the future

the various lipoproteins listed above. This information can, therefore, now be put on a caloric basis as follows:

For a restriction of 10 calories per day, the average fall in lipoprotein levels anticipated are;

1.64 mg/100ml of s_f0-12 lipoproteins
0.44 mg/100ml of s_f12-20 lipoproteins
1.85 mg/100ml of s_f20-100 lipoproteins
2.29 mg/100ml of s_f100-400 lipoproteins

The chemical composition of these lipoprotein classes is known from the work of Lindgren and associates[35]. The s_f0-12 and s_f12-20 lipoproteins contain approximately 34% cholesterol by weight; the s_f20-100 and s_f100-400 contain approximately 13% cholesterol by weight. Therefore, the overall fall in serum cholesterol level corresponding to a 10 calorie per day restriction *would be anticipated to be* $1.64 \times 0.34 + 0.44 \times 0.34 + 1.85 \times 0.13 + 2.29 \times 0.13$, or a total of *1.25 mg/100ml*. This is, of course the *average* fall anticipated, some, more sensitive than average, showing a more extensive fall in level, others, less sensitive than average, showing a less extensive fall (even including some with no change or a rise in cholesterol level).

Utilizing this simple estimate (which is extremely unlikely to be off as much as a factor or two), it can be determined how *much the Friedman accountants should have fallen in serum cholesterol* level as a result of ingesting 63 fewer calories per day during "maximal respite" than they did during "maximal stress." *If 10* calories per day results in a fall of *1.25 mg/100ml* of serum cholesterol, then 63 calories would be expected to cause a fall of 6.3x1.25, or 7.9 mg/100ml of serum cholesterol. This is to be compared with the 8 mg/100ml fall in cholesterol observed by Friedman and associates. In actual fact, the 8 mg/100ml serum cholesterol fall observed by Friedman is so uncertain, statistically, that it might really be 0 mg/100ml, or as much as 16 mg/100ml, just on a sampling basis alone. The 63 calorie per day *change in dietary consumption* for the two periods, stress and respite from stress, can easily have been from 0 calories to 100 or more calories per day, considering the "strength" of the information provided. *Therefore the dietary changes involved* can easily have accounted for the observed cholesterol changes

ease Coronary heart disease at the sub-clinical level occurs in two types of individuals,

(a) those who have never had an episode of clinical coronary heart disease. They are developing sub-clinical coronary heart disease, some at greater rates, some at lesser rates, and therefore have a greater or lesser risk of evolution of the clinical manifestations in such forms as angina pectoris, myocardial infarction, coronary insufficiency, heart failure or death.

(b) those individuals who have had a clinical manifestation of coronary heart disease in one or another form but who, during the interim period after recovery from a first, second or third clinical manifestation, can again be regarded as being in the sub-clinical phase of the disease awaiting the possibility of a recurrence of the clinical entities.

Both such groups of individuals deserve the attention of the clinician with respect to the prevention of future clinical manifestations of coronary heart disease. Who are these individuals? It has been stressed before that for group (a) *every adult in the population* is a potential candidate for future coronary heart disease Therefore, every adult in the population may be regarded as a proper patient for the treatment of sub-clinical coronary heart disease and prevention of future clinical heart disease. Indeed, unless every adult in the population is regarded as a patient in this sense serious inroads upon the mortality now claimed by coronary heart disease in its various forms will not be made Patients in the second category, group (b), namely those who have already had at least one clinical manifestation of coronary heart disease but who are now in the sub-clinical phase again, are self-evident The vast majority of these will have been under the care of a physician, who, of course, will know that they are again in the sub-clinical phase of coronary heart disease It would be deplorable to consider such patients simply as candidates for watchful waiting until a next episode of clinical coronary heart disease, or to limit advice to them to a statement that no problem exists because they have weathered their acute clinical episode. A great deal should be done for these patients, and can be done without fear of provoking cardiac neurosis Our survey in this book of features associated with

Chapter XV

THE PREVENTION OF CLINICAL CORONARY HEART DISEASE

MANY FACETS of the problems of sub-clinical coronary heart disease and the risk of future clinical manifestations have been taken up in this text. Wherever the information was deemed pertinent to the clinical task of prevention and management of coronary heart disease this was emphasized. It is the purpose of this chapter to pull together much of this information and to indicate to the clinician that an integrated program is possible today with which a highly promising effort can be made to prevent coronary heart disease. The discussions which have preceded this chapter make it abundantly clear that our knowledge of coronary heart disease is not complete. It is doubtful that, for coronary disease or any other disease, knowledge ever will be truly *complete*. But, for any disease, the more facts that are at our disposal, the more we know about the determinants of risk of the disease, the course of the disease, and about agents which influence one or another factors known to be involved in the disease, the more it becomes possible to design a reasonable program for prevention of that disease. So long as the clinician keeps an open mind with respect to the place of additional new laboratory and clinical findings, the preventive program can be modified toward improvement. In the introduction to this book it was stated that the management of clinical episodes of coronary heart disease is well covered elsewhere and is therefore not considered here. What does deserve intensive, practical consideration here is a program for applying extensive knowledge that is available and on a very solid footing toward the end of minimizing the rate of progression of sub-clinical coronary heart dis-

genic Index elevation, have much higher risks of future coronary heart disease than those characterizing an appreciable proportion of the men in the population. It would seem completely unwarranted to exclude these women from our program of preventive management even though it is true that, *on the average*, women have a lower coronary heart disease incidence rate than do men. Going further, one might choose to focus attention upon individuals over 50 years of age since the attack rate of clinical coronary heart disease is much greater above that age than it is, on the average, below that age, and it continues to rise progressively with further increase in age. In one sense concentration upon the over-50 year age group is justified by that fact of a higher attack rate of clinical disease. However, two major considerations militate against this type of approach. First, the incidence of clinical coronary heart disease is alarmingly high for persons below 50 years of age. It is especially desirable to intercept such great prematurity of this disease. Since risks can be predicted long in advance of clinical disease, it would be particularly tragic to allow markedly, excessive risks to go unnoticed and to be productive of manifest coronary heart disease below the age of 50 years. These considerations argue strongly against the exclusion of young adults from the heart disease prevention program. There are the many children who are characterized by massive lipoprotein level elevation because of hereditary defects in lipoprotein transport. Unless some effort is really made to seek them out and to alter their lipoprotein levels, their outlook is distinctly unfavorable. Perhaps an even more cogent consideration in this regard is the fact that all of the evidence concerning the mode of operation of the lipoprotein level and the blood pressure in the production of an excessive rate of development of sub-clinical coronary heart disease points strongly to *an accumulative process*. The longer this process goes on, the more disease there will be, and, since we cannot count on the exact extent of reversal of established disease that may be possible, this argues strongly in favor of a very early approach, to determine the rate at which sub-clinical coronary heart disease is developing and to intercept its development before the total accumulated disease has become too great. Wh...

increase or decrease in the incidence rate of clinical coronary heart disease has demonstrated that such effects are mediated, in the main, either by the habitual level in the blood of certain *lipoproteins, the* s_f*0-12,* s_f*12-20,* s_f*20-100,* and s_f*100-400* lipoproteins, or by the blood pressure, or by both. One factor that has not been treated here is that of coagulability of the blood, and its relationship to at least some of the clinically manifest forms of coronary heart disease. This is no oversight, but rather the result of the sketchiness of real evidence concerning the place of blood coagulability in the development of sub-clinical coronary heart disease. Some aspects of this problem will be considered below.

There is every reason to believe that vigorous attention to these two factors, the blood lipoproteins and the blood pressure, can and will make a real difference in the mortality rate of coronary heart disease. Asymptomatic elevation in blood lipoprotein levels and hence, of Atherogenic Index Value, should not be regarded as innocuous. The *absence* of symptoms characterizes the subclinical phase of coronary heart disease. However, the risk of future clinical manifestations is high with elevation in Atherogenic Index values, and with the passage of time such high risk individuals will experience all-too-many clinical episodes of coronary heart disease. Neither should asymptomatic elevation *of the blood pressure be regarded as benign,* as it has been by some workers, either in men or women. Asymptomatic elevation in blood pressure means, on the average, an increased rate *of accumulation of sub-clinical coronary heart disease* and an ultimate high risk of evolution into one of its serious, or fatal clinical manifestations.

Let us suppose one thinks of potential candidates for prevention of clinical coronary heart disease among adults in the United States population. Since men at most ages show a higher incidence rate of clinical coronary heart disease *than do women,* an initial conclusion would be that preventive medical attention should be centered upon men. To be sure, the attack rate is greater in the men so that, in one sense, *they are as a group in* greater need of preventive management. But, there are *many* women who, either because of blood pressure elevation or Athero-

tive prosecution of a program for the prevention of clinical coronary heart disease. At present a major consideration is the low degree of reliability of the values determined by many clinical laboratories, as recently reported[93], to say nothing of the methodology and standardization differences that exist from laboratory to laboratory. But were this the real essence of the difficulty with the application of the blood cholesterol measurement, steps could be taken to improve the existing situation. Methodology could be standardized and valid, reproducible techniques could be learned by essentially all clinical laboratories. However, even perfectly executed, the measurement of the blood cholesterol will fall far short of provision of the requisite information *either* for prediction or for preventive management programs. This does not mean that a blood cholesterol determination is without value Any biochemical measurement, properly performed, has intrinsic value, but the issue of real consequence is whether or not the measurement provides the necessary clinical information It is certainly true that the blood cholesterol level is related to the development of coronary heart disease. Furthermore, during the sub-clinical phase of coronary heart disease elevation of blood cholesterol level is predictive of an increased risk of future clinical coronary heart disease. But, for prediction of risk, even a perfectly executed blood cholesterol determination necessarily leads frequently to an erroneous answer concerning the patient. Why is this so? The lipoproteins which circulate in the blood *all* contain some cholesterol. Indeed the blood lipoproteins are essentially the sole source of what cholesterol is measured in a usual blood cholesterol analysis However, two points concerning the blood lipoproteins and the cholesterol they contain are central to the entire problem. These are the facts that

(1) only *certain* of the blood lipoproteins are important for coronary heart disease

(2) the content of cholesterol differs from the various lipoprotein classes

all this leads up to is the fact that no program can be regarded as medically sound if it falls short of doing two things, providing the earliest possible evaluation of the lipoprotein status and blood pressure status of young adults, preferably in the age bracket of 20-25 years. At this age an appreciable number of individuals with high risk will be discovered. Prevention has meaning for these individuals at that early age. For those who are found to show a low risk during the third decade of life are most likely to retain this favorable status, although in some instances there will be unexpected derangement of the lipoprotein levels and/or of the blood pressure as they grow older. This latter group of individuals deserves a re-check of status at intervals, perhaps, of three to five years throughout adult life

Sphygmomanometry is readily available to every physician in his office. It is of little moment whether he measures blood pressure in a reclining versus a sitting position, or with certain types of tolerance tests. What is important is that some set of reproducible conditions be achieved for the periodic blood pressure check It is evident, of course, that multiple blood pressure determinations will greatly improve the accuracy of placement of an individual on a risk scale with respect to the blood pressure. Very little is solved by the negative statement that blood pressure levels are variable for a single individual due to a variety of circumstances All experienced physicians know that they can, by repeat determination, get to know which persons show significant average trends toward elevation in the blood pressure level

The measurement of the blood lipoprotein levels and the Atherogenic Index value is also routinely available to physicians, performed by methods that have been rigorously evaluated in over 150,000 determinations No doubt some clinicians will wonder whether one of the more simple blood lipid measurements might not serve as well as a determination of the actual lipoproteins involved in the development of coronary heart disease. One such that comes into consideration is the determination of the blood cholesterol level Numerous major reasons exist which make it evident that such a determination of the blood cholesterol level will not provide the requisite information for the effec-

	Case 1 (mg/100ml)	*Case 2 (mg/100ml)*	*Case 3 (mg/100ml)*
Cholesterol Contributed From High Density Lipoproteins	300×0.13=39	300×0.13=39	300×0.13=39
From S_f12-20 Lipoproteins	60×0.34=20	60×0.34=20	60×0.34=20
From S_f0-12 Lipoproteins	400×0.34=136	300×0.34=102	200×0.34=68
From S_f20-400 Lipoproteins	100×0.13=13	200×0.13=26	300×0.13=39
Total Blood Cholesterol	208	187	166
Atherogenic Index	63 units	76 units	83 units

Here the paradoxical situation arises that the cholesterol, dropping successively from Case 1 to Case 3 predicts erroneously a successively lower risk of future clinical coronary heart disease, whereas the Atherogenic Index, rising successively from Case 1 to Case 3 predicts a successively higher risk of future clinical coronary heart disease. The source of erroneous prediction from the cholesterol measurement arises from the shift of lipoproteins relatively rich in cholesterol to lipoproteins relatively poor in cholesterol content. Hence the cholesterol level falls. However the cholesterol-poor S_f20-400 lipoproteins are even more important, milligram for milligram, than the S_f0-12 lipoproteins. Hence it is possible to have the Atherogenic Index rise as the cholesterol level falls! Levels such as are shown for Case 1 and Case 3 can be seen in a single individual during therapy. Suppose that a man started with a distribution of lipoproteins identical with that of Case 1. If a regimen of a low animal fat, high carbohydrate diet were instituted, the S_f0-12 lipoproteins will fall, in general, and the S_f20-400 lipoproteins will rise. Cases have been observed where these changes could convert a distribution such as that of Case 1 to that of Case 3. Thus the cholesterol measurement before and after institution of the dietary therapy would indicate, erroneously, a favorable response, whereas the lipoprotein Atherogenic Index measurement would indicate an unfavor-

The risk evaluation from Table XV is that the man with the Atherogenic Index value of 101 units has 14.2 over 3.24, or 4.4 times the risk of future clinical coronary heart disease that characterizes the man with an Atherogenic Index of 66 units. Thus in these two cases the blood cholesterol measurement (even if performed perfectly) is off 4.4 times in its prediction of equal risk for the two men whose cholesterol levels are both 205 mg/100ml. This cholesterol level of 205 mg/100ml is a relatively low one. Hence, a favorable prediction would be made on this basis. Yet one of the two men described with this cholesterol level has a highly unfavorable outlook and is in need of preventive medical management, a fact which would be lost sight of entirely if attention were focussed upon the low cholesterol level

THE IMPORTANCE OF THE FACT THAT LIPOPROTEINS DIFFER IN CHEMICAL COMPOSITION

In the illustrations above the obscuring effect of the high-density lipoproteins upon the prediction via blood cholesterol measurement was described Another type of difficulty operates to lead to erroneous prediction through blood cholesterol measurement, namely the differing chemical composition of lipoproteins within the s_f0 to s_f400 band. Three men may be considered with identical levels of the high density lipoproteins, e g. 300 mg/100ml Now, various possible (and observed) combinations of s_f0-12, s_f12-20, and s_f20-400 lipoproteins may be considered. Suppose for simplification s_f12-20 remains at 60 mg/100ml for all the cases to be analyzed. Suppose further that for s_f0-12 plus s_f20-400, there is a total of 500 mg/100ml Three distributions within this level of 500 mg/100ml will illustrate the problem Let the first case (Case 1) have s_f0-12 = 400 mg/100ml and s_f20-400 = 100 mg/100ml; the second case (Case 2), have s_f0-12=300 mg/100ml and s_f20-400=200 mg/100ml, and the third case, (Case 3), have 200 mg/100ml of s_f0-12 lipoproteins and 300 mg/100ml of s_f20-400 lipoproteins Now from chemical composition data for the various lipoproteins, the blood cholesterol can be calculated for cases 1, 2, and 3 and from the s_f0-12, s_f12-20, and s_f20-400 the Atherogenic Index is calculated.

genic Index should be lowered. These are hypothyroidism and diabetes mellitus.

Hypothyroidism should be searched for carefully, and should be treated effectively where present, for the elevation of S_f0-12 and S_f12-20 lipoproteins means an elevation in the Atherogenic Index and, thereby, an increase in the risk of clinical coronary heart disease. Fortunately, therapy with desiccated thyroid substance, thyroxine, or tri-iodo-thyronine is specific therapy and will effect a lowering in lipoprotein level as a concomitant of correction of the hypothyroidism Some patients present more occult problems referable to the thyroid status Where clinical hypothyroidism is suspected as a possible diagnosis and where S_f0-20 lipoproteins are elevated, but where other laboratory measurements of thyroid function are equivocal, a trial of thyroid therapy is clearly indicated There are, further, a large number of persons in the population who, at one time or another, have had ablative treatment of their thyroid gland by surgery, radiation, or by chemical means To be sure, frank clinical myxedema is not a common residual effect of surgical treatment of hyperthyroidism Nevertheless persons who have had ablative therapy to their thyroid may suffer elevation of S_f0-12 and S_f12-20 lipoprotein levels Even in the absence of clinical hypothyroidism such persons deserve a trial of thyroid replacement therapy.

Diabetes mellitus presents the second special situation of real consequence Of course, first of all diabetes itself must be controlled clinically Thereafter attention must be directed toward any excessive risk of coronary heart disease a particular diabetic may have as a result of lipoprotein-Atherogenic Index elevation The discussion of diabetes in Chapter XII and the data of Table XLV indicate strongly that chemical control of diabetes (even within the clinical state free of acidosis) is of real importance in determination of the lipoprotein status. Therefore, within the limits imposed by patient intelligence, life circumstances, and the prevention of hypoglycemic episodes, hyperglycemia and glycosuria should be minimized The evidence in Table XLV gives the average improvement in Atherogenic Index values with increase in the control of hyperglycemia. It follows that some diabetics will experience much greater than average

able response, which is correct. The use of the familiar rice diet is a case in point, where precisely this type of situation arises and where the blood cholesterol would indicate the direction of the response *opposite* to what is truly occurring in the patient. Probably the major reason why this type of patient on a rice diet does not fare as badly, on the average, as the Atherogenic Index trends would suggest, is that the rice diet regimen as practised is associated with a favorable fall in diastolic blood pressure.

THE PLANNING OF A PREVENTIVE REGIMEN FOR INDIVIDUAL PATIENTS

For those patients whose overall risk of coronary heart disease is low or moderate, *when calculated by multiplication of the* risk arising from Atherogenic Index value by that arising from diastolic blood pressure, the best program is simple notification of the patient that he is a fortunate person characterized by a low risk of future coronary heart disease. No specific measures are indicated. Where the overall risk is elevated, from elevated blood pressure with or without Atherogenic Index elevation, it is definitely indicated that a program be directed toward lowering such elevated blood pressure. This is true even though the blood pressure elevation is asymptomatic at the time of study. The entire subject of the most efficacious procedures for controlling elevation in blood pressure is a major subject in itself, a subject covered elsewhere in sources available to physicians. Where the risk is elevated from elevation in Atherogenic Index with or without diastolic blood pressure elevation, there is a definite indication for a program directed toward the lowering of the elevated Atherogenic Index values. The approach to this problem for an individual patient deserves amplification.

THE PROGRAM FOR LOWERING ELEVATED ATHEROGENIC INDEX VALUES

Special Situations

Two special situations must be commented upon before consideration of the person in the population-at-large whose Athero-

DIETARY APPROACH TO ATHEROGENIC INDEX LOWERING IN THE OVERWEIGHT PERSON

The overweight person shows, on the average, an appreciable elevation of the Atherogenic Index value (See Chapter IX). Further in those overweight persons who demonstrate elevation in blood lipoprotein levels and Atherogenic Index values the correction of overweight via a decrease in habitual calorie intake provokes a fall in Atherogenic Index value, which is maintained if the person does not return to his habitually high calorie intake. The "natural" experiment described in Chapter IX provides us with very reasonable working data for the clinician to use in planning a regimen for the overweight person. Under the usual circumstances of living, a cross-section of individuals, described in Chapter IX, either lost or gained weight spontaneously during a one to two year period. The lipoproteins and Atherogenic Index increased, on the average, for those who gained weight and decreased on the average for those who lost weight. From these data the average changes in level that can be anticipated for the various lipoprotein classes and for the Atherogenic Index value per unit change in daily calorie intake were calculated (See Chapter XIV). These values are as follows;

For a reduction of 10 calories per day in habitual caloric intake, *on the average,*

S_f 0-12 lipoprotein levels fall	1.6 mg/100ml
S_f 12-20 lipoprotein levels fall	0.4 mg/100ml
S_f 20-100 lipoprotein levels fall	1.8 mg/100ml
S_f 100-400 lipoprotein levels fall	2.3 mg/100ml
Atherogenic Index Values fall	0.95 units

The clinician may utilize such data directly in planning a long-term regimen for the overweight person. This may be illustrated by consideration of a specific case of an overweight man of 35 years of age whose Atherogenic Index value is 120 units, a value that corresponds to an appreciable elevation in risk of future clinical coronary heart disease. The physician would be desirous of lowering such a value to 80 Atherogenic Index units, if possible, or perhaps more. What caloric restriction is needed? If 10 calories per day corresponds to an average lowering in Atherogenic Index of 0.95 units, then the required caloric restriction

41 Glazier, F., Tamplin, A., Strisower, B., deLalla, O., Gofman, J., Dawber, T., and Phillips, E.: Human Serum Lipoprotein Concentrations. *Journal of Gerontology*, 9 395, 1954.

42 Dublin, L.: The Influence of Weight on Certain Causes of Death *Human Biology*, 2 159, 1930

43 Symonds, B The Blood Pressure of Healthy Men and Women. *Journal of the American Medical Association*, 80.232, 1923

44. Short, J J, and Johnson, H. J: [illegible] of Overweight on Blood Pressures of Healthy [illegible] or Periodic Health Examination. [illegible] 0, 1939

45 Faber, A Readings of Blood Pressure of 1000 Healthy Individuals aged 20 25 years *Skandinav Arch. f Physiol*, 45·189, 1924

46 Nichols, A V., Dobbin, V, and Gofman, J W.: *Influence of Dietary Factors* upon Human Serum Lipoprotein Concentrations. *Geriatrics*, 12 7, 1957.

47. Preble, W E. Obesity, Observation of One Thousand Cases. *Boston Medical and Surgical Journal*, 18 617, 1923

48. Adlersberg, D, Coler, H. R, and Lasal, J. Effect of Weight Reduction on Course of Arterial Hypertension *Journal of the Mount Sinai Hospital*, 12 984, 1946.

49. Bauman, L Obesity, Recent Reports in the Literature and Results of Treatment *Journal of the American Medical Association*, 90 22, 1929.

50 Terry A J, Jr Obesity and Hypertension *Journal of the American Medical Association*, 81 1283, 1923

51 Moschcowitz, E· Essays on the Biology of Disease, Obesity. *Journal of the Mount Sinai Hospital*, 11 357, 1945

52 Dublin, L and Marks, H *Mortality Among Insured Overweights in Recent Years* Read at the 60th Annual Meeting of the Association of Life Insurance Medical Directors of America, October 11-12, 1951

53 Cullumbine H *Cardiovascular Disease in Ceylon in Factors Regulating Blood Pressure* Transactions of the Fifth Conference, New York, New York, Josiah Macy, Jr Foundation, 1951, p 124

54 Bronte Stewart, B., Keys, A, and Brock, J F· Serum Cholesterol, Diet, and Coronary Heart Disease An Inter-Racial Survey in the Cape Peninsula *Lancet*, 2 1103, 1955

55 Larsen, N P The Animal Fat Diet and Atherosclerosis *Hawaii Medical Journal*, 14 485, 1955

56 Snapper, I *Chinese Lessons to Western Medicine* New York, New York, Interscience Publishers, Inc 1941, p 10

57 Hatch, F, Abell, L, and Kendall, F: Effects of Restriction of Dietary Fat and Cholesterol Upon Serum Lipids and Lipoproteins in Patients with Hypertension *American Journal of Medicine*, 19 48, 1955

58 Ahrens, E. J., Jr Nutritional Factors and Serum Lipid Levels *American Journal of Medicine*, XXIII 928, 1957.

59 Walker W J, Weiner, N, and Milch, L. J Differential Effect of Dietary Fat and Weight Reduction on Serum Levels of Beta Lipoproteins. *Circulation*, XV 31, 1957

60 Kinsell, L W, Partridge, J, Boling, L, Margen, S, and Michaels, G.: Dietary Modification of Serum Cholesterol and Phospholipid Levels. *Journal of Clinical Endocrinology*, 12.909, 1952.

21. Heptinstall, R. H., and Porter, K. A.: The Effect of a Brief Period of High Blood Pressure on Cholesterol-Induced Atheroma in Rabbits. *British Journal of Experimental Pathology, XXXVIII*:55, 1957.

22. Yater, W., Traum, A., Brown, W., Fitzgerald, R., Geisler, M., and Wilcox, B.: Coronary Artery Disease in Men 18-39 Years of Age. Report of 866 cases, 450 with Necropsy Examination. *American Heart Journal, 36*:334, 1948.

23. Dawber, T. R., Moore, F. E., and Man, G. V.: Measuring the Risk of Coronary Heart Disease in Adult Population Groups II. Coronary Heart Disease in the Framingham Study. *American Journal of Public Health, 47*:4, 1957.

24. Wright, I. S., Marple, C. D., and Beck, D. F.: *Myocardial Infarction—Its Clinical Manifestations and Treatment with Anticoagulants.* New York, Grune and Stratton, 1954, p. 45.

25. Master, A. M., Garfield, C. I., and Walters, M. B.: *Normal Blood Pressure and Hypertension.* Philadelphia, Pennsylvania, Lea and Febiger, 1952. p. 126.

26. Levine, S. A., and Brown, C. L.: Coronary Thrombosis: its Various Clinical Features. *Medicine, 8*:245, 1929.

27. Chambers, W. N.: Acute Myocardial Infarction. A Study of 100 Consecutive Cases. *New England Journal of Medicine, 235*:347, 1946.

28. Doscher, N., and Poindexter, C. A.: Myocardial Infarction without Anticoagulant Therapy. Deaths, Emboli and an Analysis of Factors Influencing Mortality. *American Journal of Medicine, 8*:623, 1950.

29. Mintz, S. S. and Katz, L. N.: Recent Myocardial Infarction. An Analysis of 572 Cases. *Archives of Internal Medicine, 80*:205, 1948.

30. Fisher, R.: The Use of Multiple Measurements in Taxonomic Problems. *Eugenics, 7*:179, 1936.

31. Gofman, J. W., Strisower, B., deLalla, O., Tamplin, A., Jones, H. B., and Lindgren, F.: Index of Coronary Artery Atherogenesis. *Modern Medicine* June 15, 119, 1953.

32. Gofman, J. W., Rubin, L., McGinley, J., and Jones H. B.: Hyperlipoproteinemia. *American Journal of Medicine, 17*:514, 1954.

33. Wilkinson, C. F., Hand, E. A., and Fliegelman, M. J.: Essential Familial Hypercholesterolemia. *Annals of Internal Medicine, 29*:671, 1948.

34. Piper, J., and Orrlid, L.: Essential Familíal Hypercholesterolemia and Xanthomatosis. Followup study of Twelve Danish Families. *American Journal of Medicine, 21*:34, 1956.

35. Lindgren, F. T., and Gofman, J. W.: The Role of Lipoproteins in Coronary Disease. *Bulletin of the Swiss Academy of Medical Sciences, 13*:152, 1957.

36. Gertler, M. M., and White, P. D.: *Coronary Heart Disease in Young Adults,* Cambridge, Massachusetts, Harvard University Press, 1954. P. 22.

37. Gofman, J. W., Kovich, E. L., deLalla, O. F.: The Relationship of Family History with Serum Lipoprotein Levels and Coronary Heart Disease Risk. To be published.

38. Gofman, J. W., and deLalla, O.: Serum Lipoprotein Levels in Clinical States Other than those Associated with Atherosclerosis. To be published.

39. Tamplin, A., Strisower, B., deLalla, O., Gofman, J., and Glazier, F.: Lipoproteins, Aging, and Coronary Artery Disease. *Journal of Gerontology, 9*:404, 1954.

40. Bevans, M., Davidson, J. O., and Kendall, F. E.: Regression of Lesions in Canine Arteriosclerosis. *Archives of Pathology, 51*:288, 1951.

78. Strisower, E., Weed, R., Gofman, J., Strisower, B., and deLalla, O.: The Effect of Insulin on Serum Lipoproteins of Diabetic Patients. Presented before the Endocrine Society, June 20, 1958, San Francisco, California (To be published)
79. Strisower, B., Gofman, J. W., Galioni, E., Rubinger, J. H., O'Brien, G. W., and Simon, A.: Effect of Long-Term Administration of Desiccated Thyroid on Serum Lipoprotein and Cholesterol Levels. *Journal of Clinical Endocrinology and Metabolism, XV*:73, 1955.
80. Strisower, B., Elmlinger, P., Gofman, J., and deLalla, O.: The Effect of l-Thyroxine on Serum Lipoproteins and Serum Cholesterol Concentrations. Presented American Goiter Association June 19, 1958, San Francisco, California (To be published)
81. Strisower, E., Gofman, J., Strisower, B., and deLalla, O.: Physiologic Effects of l-Triiodothyronine. In press in *Journal of Clinical Endocrinology and Metabolism*
82. Blumgart, H. L., Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris. The Therapeutic Effect on Thyroidectomy on Patients without Clinical or Pathologic Evidence of Thyroid Toxicity. *Archives of Internal Medicine, 52*:165, 1933.
83. Blumgart, H. L., Freedberg, A. S., and Kurland, G. S.: Hypercholesterolemia, Myxedema, and Atherosclerosis. *American Journal of Medicine, 14*:665, 1953.
84. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., and Nichols, A. V.: Lipoproteins in Atherosclerosis. *American Journal of Medicine, XI*:358, 1951.
85. Strisower, B., Gofman, J., Galioni, E. F., Rubinger, J. H., Pontau, Jr., and Guzvich, P.: Long Term Effect of Dried Thyroid on Serum Lipoproteins and Serum Cholesterol Levels. *Lancet, I*:120, January 19, 1957.
86. Goolden, A. W. B.: Physiological Activity of Tetraiodo-thyroacetic acid. *Lancet, I*:890, June 9, 1956.
87. Editorial: Thyroid Hormones in Coronary Disease. *Lancet, I*:896, June 9, 1956.
88. Morris, J. N., Heady, J., Raffle, P. H. B., Roberts, C. G., and Parks, J. W.: Coronary Heart Disease and Physical Activity of Work. *Lancet, 265*:1053 and 1111, 1953.
89. Hammarsten, J. F., Cathey, C. W., and Wolf, S.: Serum Cholesterol, Diet, and Stress in Patients with Coronary Artery Disease. *Journal of Clinical Investigation, 36*:897, 1957.
90. Groover, M. E.: *Clinical Evaluation of a Public Health Program to Prevent Coronary Artery Disease*. The Mary Scott Newbold Lecture. Delivered before American College of Physicians, Philadelphia, Pennsylvania, 1957.
91. Friedman, M., and Rosenman, R. H.: Comparison of Fat Intake of American Men and Women. Possible relationship to incidence of clinical coronary artery disease. *Circulation, XVI*:339, 1957.
92. Friedman, M., Rosenman, R., and Carroll, V.: Changes in the Serum Cholesterol and Blood Clotting Time in Men Subjected to Cyclic Variation of Occupational Stress. *Circulation, XVII*:852, 1958.
93. Rivin, A. U., Yoshino, A. B., Shickman, M., and Schjeide, O. A.: Serum Cholesterol Measurement Hazards in Clinical Interpretation. *Journal of the American Medical Association, 166*:2108, 1958.
94. Barr, D. P.: Some Chemical Factors in the Pathogenesis of Atherosclerosis. *Circulation, VIII*, 1953.

61. Ahrens, E. H, Tsaltas, T. T., Hirsch, J, and Insull, W, Jr: Effect of Dietary Fats on the Serum Lipids of Human Subjects *Journal of Clinical Investigation, 34*:918, 1955.

62. Lindgren, F. T., Nichols, A V, and Freeman, N. K.: Physical and Chemical Composition Studies on the Lipoproteins of Fasting and Heparinized Human Sera *Journal of Physical Chemistry, 59* 930, 1955.

63 Beveridge, J M. R, Connell, W F, and Mayer, G A: Dietary Factors Affecting the Level of Plasma Cholesterol in Humans, the Role of Fat *Canadian Journal of Biochemistry and Physiology, 34*:441, 1956.

64. Perkins, R., Wright, I. S, and Gatze, B W: Effect of Safflower Oil Emulsion on Serum Cholesterol Levels in Young Adult Males. *Journal of the American Medical Association, 166* 2132, 1958.

65. Ahrens, E. J, Jr, Hirsch, J, Insull, W Jr, Tsaltas, T T, Blomstrand, R., and Peterson, M L: The Influence of Dietary Fats on Serum Lipid Levels in Man *Lancet, 1*:943, 1957.

66. Bronte-Stewart, B., Antonis, A, Eales, L, and Brock, J F. Effect of Feeding Different Fats on the Serum Cholesterol Level. *Lancet, 1* 521, 1956

67 Hammond, E C, and Horn, D. The Relationship Between Human Smoking Habits and Death Rates. *Journal of the American Medical Association, 155* 1316, 1954

68 Gofman, J W, Lindgren, F T, Strisower, B, deLalla, O, Glazier, F. and Tamplin, A Cigarette Smoking, Serum Lipoproteins, and Coronary Heart Disease *Geriatrics, 10*:349, 1955.

69 Roth, G M: *Tobacco and the Cardiovascular System* Springfield, Illinois, Charles C Thomas, 1951, p 31

70. Hammond, E. C., and Horn, D: Smoking and Death Rates—Report on Forty-Four Months of Follow-up of 187,783 Men *Journal of the American Medical Association, 166* 1159, 1958

71. Kolb, F, deLalla, O, and Gofman, J. W. The Hyperlipemias in Disorders of Carbohydrate Metabolism Serial Lipoprotein Studies in Diabetic Acidosis with Xanthomatosis and in Glycogen Storage Disease *Metabolism, IV* 310, 1955

72. Gofman, J W., deLalla, O. Glazier, F Freeman, N K, Lindgren, F T, Nichols, A V, Strisower, B, and Tamplin, A R The Serum Lipoprotein Transport System in Health, Metabolic Disorders, Atherosclerosis, and Coronary Heart Disease *Plasma, II* 413, 1954

73 Moore, R A *Textbook of Pathology* Philadelphia, Pennsylvania W B Saunders Company, 1945 p 1091

74 Master, A M, Dack, S, and Jaffe, H L. Age, Sex, and Hypertension in Myocardial Infarction due to Coronary Occlusion *Archives of Internal Medicine, 64* 767, 1939

75 Wilkerson, H L C and Krall, L P. Diabetes in a New England Town A study of 3516 Persons in Oxford, Massachusetts *Journal of the American Medical Association, 135* 209, 1947

76. Keiding, N R, Mann, G V, Root, H F, Lowry, E Y, and Marble A Serum Lipoprotein and Cholesterol Levels in Normal Subjects and Young Patients with Diabetes in Relation to Vascular Complications *Diabetes, 1* 434, 1953

77 Engelberg, H, Gofman, J. W, and Jones, H B Serum Lipids and Lipoproteins in Diabetic Glomerulosclerosis *Metabolism, I*:300, 1952

INDEX

95 Gofman, J. W., and deLalla, O. F.: High Density Lipoproteins in Coronary Heart Disease. To be published.

96 Eilert, M. L.: The Effect of Estrogens Upon the Partition of the Serum Lipids in Female Patients. *American Heart Journal, 38*:472, 1949.

97. Barr, D. P., Russ, E. M., and Eder, H. A.: Influence of Estrogens on Lipoproteins in Atherosclerosis. *Transactions of the American Association of Physicians 65*:102, 1952.

98. Steiner, A., Payson, H., and Kendall, F. E.: Effect of Estrogenic Hormone on Serum Lipids in Patients with Coronary Arteriosclerosis. *Circulation, XI* 784, 1955.

99 Marmorston, J., Moore, F., and Lewis, J. Effect of Ethinyl Estradiol Upon Serum Lipoprotein Levels and Atherogenic Index Values in Male Survivors of Myocardial Infarction. Personal Communication, May, 1958

100. Cooper, Elmer E.: Sex Hormones and Atherogenesis. *American Practitioner and Digest of Treatment, 7*:436, 1956

101. Hahn, P.: Abolishment of Alimentary Lipemia following Injection of Heparin. *Science, 98* 19, 1943.

102 Graham, D., Lyon, T., Gofman, J., Jones, H., Yankley, A., Simonton, J., and White, S. Blood Lipids and Human Atherosclerosis II. The Influence of Heparin Upon Lipoprotein Metabolism. *Circulation, IV* 666, 1951.

103. Shore, B., Nichols, A., and Freeman, N.: Evidence for Lipolytic Action by Human Plasma Obtained After Intravenous Administration of Heparin. *Proceedings of the Society of Experimental Biology and Medicine, 83*:216, 1953

104. Engelberg, H., Kuhn, R., and Steinman, M.: A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Atherosclerosis. *Circulation, 13* 489, 1956.

105. Peterson, D. W. Effect of Soy Bean Sterols in the Diet on Plasma and Liver Cholesterol in Chicks. *Proceedings of the Society for Experimental Biology and Medicine, 78*:143, 1951.

106. Best, M. M., Duncan, C. H., Van Coon, E. J., and Wathen, J. D. Lowering of Serum Cholesterol by the Administration of a Plant Sterol. *Circulation, X*: 201, 1954

107. Farquhar, J. W., Smith, R. E., and Dempsey, M. E.: The Effect of Beta Sitosterol on the Serum Lipids of Young Men with Arteriosclerotic Heart Disease. *Circulation, XIV*:77, 1956.

108. Altschul, R., Hoffer, A., and Stephen, J. D. Influence of Nicotinic Acid on Serum Cholesterol in Man. *Archives of Biochemistry, 54* 558-559, 1955

109 Parsons, W. B., Jr., Achor, R. W. P., Berge, K. G., McKenzie, B. F., and Barker, N. W.: Changes in Concentration of Blood Lipids Following Prolonged Administration of Large Doses of Nicotinic Acid to Persons with Hypercholesterolemia. *Proceedings of the Staff Meeting of the Mayo Clinic, 31* 377, 1956

110. Parsons, W. B., Jr., and Flinn, J. H.: Reduction in Elevated Blood Cholesterol Levels by Large Doses of Nicotinic Acid. *Journal of the American Medical Association, 165* 234, 1957.

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